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USMLE® STEP 2 CK

Clinical Knowledge

Eleventh Edition

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STUDENT GUIDE

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Rapid review section for last minute cramming

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FIRST AID FOR THE® USMLE Step 2 CK

Eleventh Edition

TAO LE, MD, MHS
Founder, ScholarRx
Associate Clinical Professor, Department of Medicine
University of Louisville School of Medicine

VIKAS BHUSHAN, MD
Founder, *First Aid for the USMLE Step 1*
Boracay, Philippines

MONA ASCHA, MD
Fellow, Department of Plastic Surgery
Johns Hopkins University

ABHISHEK BHARDWAJ, MD
Pulmonologist and Intensivist
Coast Pulmonary Associates, Orange County, California
Assistant Clinical Professor, Health Sciences
University of California, Riverside

MARINA BOUSHRA, MD
Emergency Medicine and Critical Care Medicine
Cleveland Clinic Foundation, Cleveland, Ohio

DANIEL GRIFFIN, DO
Intensivist, Saint Francis Medical Center

CAROLINE COLEMAN, MD
Resident, Department of Medicine
Emory University School of Medicine

STEPHANIE JONES, PhD
Emory University Laney Graduate School

KIMBERLY KALLIANOS, MD
Assistant Professor, Department of Radiology and Biomedical Imaging
University of California, San Francisco School of Medicine

Mc Graw Hill

New York Chicago San Francisco Athens London Madrid Mexico City
Milan New Delhi Singapore Sydney Toronto

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DEDICATION

To the contributors to this and past editions, who took
time to share their knowledge, insight, and humor for
the benefit of students and physicians everywhere.

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About the Authors

CONTRIBUTING AUTHORS

Manik Aggarwal, MD, MBBS
Fellow, Gastroenterology and Hepatology
Mayo Clinic, Rochester, Minnesota

John Carl Barba II, MPH
MD Candidate
Ohio State University College of Medicine

Anup Chalise, MBBS, MS
Nepal

Paola Ghanem, MD
Physician, Department of Internal Medicine
Johns Hopkins University

Myles Mowery, DO, MBA
Resident, Diagnostic and Interventional Radiology
Spectrum Health/Michigan State University
Grand Rapids, Michigan

Waneeza Mughees, MD
Resident, Obstetrics and Gynecology
Drexel University College of Medicine, Philadelphia

Christian Cuvillier Padilla, MD
Chief Resident, Internal Medicine
Cleveland Clinic and Cleveland Veterans Affairs Medical Center, Cleveland, Ohio

Vivek Podder, MBBS
Intern
BIRDEM General Hospital, Bangladesh

Vikram Shee, MBBS, MSc
Physician Case Manager
Teladoc Health, Inc.

Collin Andrew Weintraub, MD
Resident, General Surgery
State University of New York Upstate Medical University

IMAGE AND ILLUSTRATION TEAM

Yoree Grace Chung
MD/PhD Candidate
Emory University School of Medicine

Nikitha Crasta, MBBS
Mangalore, India

Sean Evans, MD
Resident, Internal Medicine
Emory University School of Medicine

Victor Jose Martinez Leon, MD
Resident, Internal Medicine
Einstein Medical Center, Philadelphia

Angel Xiao, MD, MSE
Resident, Orthopedic Surgery
University of California–San Francisco

ASSOCIATE AUTHORS

Aparna Savitri Bhat, MD
Fellow, Pulmonary and Critical Care Medicine
Cleveland Clinic, Cleveland, Ohio

Naveena Daram, MD
Resident, Obstetrics and Gynecology
Wright State University

Ifrah Fatima, MBBS
Resident, Internal Medicine
University of Missouri–Kansas City School of Medicine

Lindsay Friedman, MD, MS
Resident, General Surgery
Rush University Medical Center

Luise Josefine Froessl, MD
Resident
Université d'Aix-Marseille, Faculté de Medecine

Izhan Hamza, MBBS
Resident
University of Texas Medical Branch, Internal Medicine

Abdul Rehman Mustafa, MBBS
Alfaisal University College of Medicine, Saudi Arabia

Aaron Panicker, MD
Resident, Emergency Medicine
University of Florida College of Medicine

Austin Patrick, DO
Resident
Franciscan Health Olympia Fields

Faateh Ahmad Rauf, MBBS
CMH Lahore Medical College and Institute of Dentistry, Pakistan

Jaimie Rogner, MD, MPH
Resident, Internal Medicine/Pediatrics
University of Rochester Medical Center/Strong Memorial Hospital

Kyle Robert Wagner
MD Candidate
University of Illinois College of Medicine, Peoria

FACULTY REVIEWERS

Brooks D. Cash, MD
Professor, Department of Medicine
Chief, Gastroenterology, Hepatology, and Nutrition
University of Texas Health Science Center at Houston

Dimitri Cassimatis, MD
Associate Professor, Department of Medicine
Emory University School of Medicine

Bradley Cole, MD
Assistant Professor of Neurology
Loma Linda University School of Medicine

Meredith K. Greer, MD
Assistant Professor, Department of Medicine
Emory University School of Medicine

Jennifer O. Howell, MD
Associate Professor, Department of Obstetrics and Gynecology
Duke University Medical Center

Matthew Kraybill, PhD
Clinical Neuropsychologist
Cottage Health, Santa Barbara, California

Patrick M. Lank, MD, MS
Assistant Professor, Department of Emergency Medicine
Northwestern University, Feinberg School of Medicine

Kachiu C. Lee, MD, MPH
Assistant Professor (Adjunct), Department of Dermatology
Lewis Katz School of Medicine at Temple University

Carl Marfurt, PhD
Professor Emeritus, Department of Anatomy, Cell Biology and Physiology
Indiana University School of Medicine–Northwest, Gary

Peter Marks, MD, PhD
Center for Biologics Evaluation and Research
US Food and Drug Administration

Kristen L. Pagel, MD, MPH
Assistant Professor, Department of Psychiatry
University of Utah School of Medicine

Mahesh Patel, MD

Professor, Department of Medicine
University of Illinois at Chicago College of Medicine

Diane Payne, MD, MPT
Orthopedic, Hand and Microvascular Surgery
OrthoAtlanta Newnan, Georgia

Soroush Rais-Bahrami, MD
Professor of Urology and Radiology and Interim Chair, Department of Urology
University of Alabama at Birmingham School of Medicine

Keisha Ray, PhD
Assistant Professor, McGovern Center for Humanities and Ethics
University of Texas Health Science Center at Houston

Rachel Marie E. Salas, MD, MEd
Professor, Neurology and Nursing
Johns Hopkins Medicine

Sarah Schimansky, MB BCh BAO
Resident, Department of Ophthalmology
Bristol Eye Hospital

Shireen Madani Sims, MD
Associate Professor and Vice Chair for Education, Obstetrics and Gynecology
University of Florida College of Medicine

Nathan Wm. Skelley, MD
Associate Professor, Medical Director of Orthopaedic Surgery
Sanford Health–University of South Dakota School of Medicine

Matthew Sochat, MD
Physician, Hematology/Oncology
Southeastern Medical Oncology Center

Lorrel Toft, MD
Associate Professor of Cardiology, Department of Medicine
University of Nevada, Reno School of Medicine

Tisha Wang, MD
Professor of Clinical Medicine, Department of Medicine
David Geffen School of Medicine at UCLA

Sylvia Wassertheil-Smoller, PhD
Professor Emerita, Department of Epidemiology and Population Health
Albert Einstein College of Medicine

Adam Weinstein, MD
Associate Professor of Medical Sciences and Pediatrics
Frank H. Netter MD School of Medicine at Quinnipiac University

James S. Yeh, MD, MPH
Department of Medicine
Massachusetts General Hospital, Harvard Medical School

Kristal Young, MD
Clinical Instructor, Department of Cardiology
Huntington Hospital, Pasadena, California

Preface

With the 11th edition of *First Aid for the USMLE Step 2 CK*, we continue our commitment to providing students with the most high-yield and up-to-date preparation guide for the USMLE Step 2 CK exam. Preparation for and performance on the Step 2 CK exam are more important than ever with the transition of the Step 1 exam to a pass/fail scoring system in 2022. With this in mind, we have greatly expanded the content and depth for the 11th edition. This revision includes:

- Over 200 additional pages of content incorporating the most current evidence-based reviews and recommendations to help students on the Step 2 CK exam and in clinical practice.
- 163 new and revised diagrams and illustrations, including more than 40 new diagnostic and management algorithms, to further drive home the next best diagnostic and management options.
- 140 new and revised photos/images to help visualize various disorders, descriptive findings, and clinical content tie-ins.
- Extensive text revisions, new mnemonics, and clarifications curated by a team of 26 medical student and resident physician authors who excelled on their USMLE exams and verified by a team of expert faculty advisors and nationally recognized USMLE instructors.
- Continued focus on clinical presentation and the best initial step in diagnosis and management, mirroring the content outline and blueprint of Step 2 CK.
- Vignette-style flash cards embedded in the margins to reinforce key concepts.
- Heavily updated and revised Rapid Review section for last-minute preparation.
- Revised rating of current high-yield review resources, with clear explanations of their relevance to Step 2 CK exam review.
- Improved organization and integrations of text, illustrations, clinical images, tables, and algorithms throughout for focused review of high-yield topics.

The 11th edition of *First Aid for the USMLE Step 2 CK* truly is a completely revised, in-depth, student-to-student guide for preparation for the Step 2 CK exam. The 11th edition would not have been possible without the help from hundreds of students and faculty members who contributed their feedback and suggestions. We invite students and faculty to continue sharing their thoughts and ideas to help us improve *First Aid for the USMLE Step 2 CK* (see How to Contribute, p. xi).

Tao Le
Louisville

Vikas Bhushan
Boracay

Mona Ascha
Baltimore

Abhishek Bhardwaj
Orange County

Marina Boushra
Cleveland

Daniel Griffin
Cape Girardeau, Missouri

Caroline Coleman
Atlanta

Stephanie Jones
Tumwater, Washington

Kimberly Kallianos
San Francisco

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Tao Le
Louisville

Vikas Bhushan
Boracay

Mona Ascha
Baltimore

Abhishek Bhardwaj
Orange County

Marina Boushra
Cleveland

Daniel Griffin
Cape Girardeau, Missouri

Caroline Coleman
Atlanta

Stephanie Jones

Tumwater, Washington

Kimberly Kallianos
San Francisco

How to Contribute

In our effort to continue to produce a high-yield review source for the Step 2 CK exam, we invite you to submit any suggestions or corrections. We also offer paid internships in medical education and publishing ranging from three months to one year (see below for details). Please send us your suggestions for the following:

- Study and test-taking strategies for the Step 2 CK exam
- New high-yield facts, mnemonics, diagrams, and illustrations
- Low-yield topics to remove

For each entry incorporated into the next edition, you will receive up to a $20 gift certificate to Amazon as well as personal acknowledgment in the next edition. Diagrams, tables, partial entries, updates, corrections, and study hints are also appreciated, and significant contributions will be compensated at the discretion of the authors. Also let us know about material in this edition that you feel is low yield and should be deleted.

The preferred way to submit entries, suggestions, or corrections is via our blog:

www.firstaidteam.com

We are also reachable by e-mail at **firstaid@scholarrx.com**.

NOTE TO CONTRIBUTORS

All entries become property of the authors and are subject to editing and reviewing. Please verify all data and spellings carefully. If similar or duplicate entries are received, only the first entry received will be used. Include a reference to a standard textbook to facilitate verification of the fact. Please follow the style, punctuation, and format of this edition if possible.

INTERNSHIP OPPORTUNITIES

The author team is pleased to offer part-time and full-time paid internships in medical education and publishing to motivated physicians. Internships may range from three months (eg, a summer) up to a full year. Participants will have an opportunity to author, edit, and earn academic credit on a wide variety of projects, including the popular *First Aid* series. Writing/editing experience, familiarity with Microsoft Word and Google Docs, and illustration skills are highly desired. For more information, e-mail a résumé or a short description of your experience along with a cover letter to **firstaidteam@usmle-rx.com**.

How to Use This Book

We have made many improvements and added several new features to this edition of *First Aid for the USMLE Step 2 CK*. In particular, we have added more than two hundred pages of content and hundreds of new illustrations and images throughout the text to facilitate studying. We encourage you to read all aspects of the text to learn the material in context. We have also included comments in the margins and vignette questions to periodically test your knowledge of key concepts. These questions are located in the lower corner of certain pages. To prevent peeking at the answers, you'll find the answer on the back of the same page in the lower corner. These questions are not always representative of test questions.

To practice for the exam and simulate the actual test day, you can use the *USMLE-Rx Step 2 CK Qmax* question test bank (www.usmle-rx.com). If you are constantly on the move, use the *USMLE-Rx Step 2 CK* app. The question bank and this text are more than enough to allow many students to ace the exam.

Good luck!

SECTION 1

GUIDE TO EFFICIENT EXAM PREPARATION

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INTRODUCTION

The United States Medical Licensing Examination (USMLE) Step 2 allows you to pull together your clinical experience on the wards with the numerous “factoids” and classical disease presentations that you have memorized over the years. Where Step 1 stresses basic disease mechanisms and principles, Step 2 places more emphasis on clinical diagnosis and management, disease pathogenesis, and preventive medicine. Previously, the Step 2 examination consisted of the Step 2 Clinical Knowledge examination (Step 2 CK), and the Step 2 Clinical Skills examination (Step 2 CS). However, recent changes have removed the

Step 2 CS exam as a requirement for ECFMG certification after the onset of the pandemic, and this change has been recorded as permanent by the ECFMG.

The USMLE Step 2 CK is the second of three examinations that you must pass to become a licensed physician in the United States. The computerized Step 2 CK is a 1-day (9-hour) multiple-choice examination.

KEY FACT

The goal of the Step 2 CK is to apply your knowledge of medical facts to clinical scenarios that you may encounter as a resident.

USMLE STEP 2 CK—COMPUTER-BASED TESTING BASICS

WHO CAN REGISTER FOR THE EXAM?

The eligibility requirement for USMLE Step 2 CK exam is same as that of USMLE Step 1 and can be taken either before or after the Step 1 exam. This means that you should be:

- Officially enrolled in, or be a graduate of, a US or Canadian medical school leading to the MD degree (LCME accredited), or
- Officially enrolled in, or be a graduate of, a US medical school leading to the DO degree (COCA accredited), or
- Officially enrolled in, or be a graduate of, a medical school outside the US and Canada and listed in the World Directory of Medical Schools as meeting ECFMG eligibility requirements and meet other ECFMG criteria.

These criteria should be met at the time of application and on the test day.

HOW WILL THE CBT BE STRUCTURED?

The Step 2 CK exam is a computer-based test (CBT) administered by Prometric, Inc. It is a 1-day examination with a maximum of 318 items divided into eight 1-hour blocks that are administered during a single 9-hour testing session. The number of items in a block are displayed at the beginning of each block. This number may vary from block to block but will not exceed 40 items per block.

Two question styles predominate throughout. The most common format is the **single one-best-answer** question. This is the traditional multiple-choice format in which you are tasked with selecting the “most correct” answer. **Sequential item sets** comprises the second question style. These are sets of multiple-choice questions that are related and must all be answered in sequence without skipping a question in the set. As you answer questions in a set, the previous answers become locked and cannot be changed. These are the only questions on the USMLE examination that are locked in such a way. There are no more than five sequential item sets within each USMLE Step 2 CK exam.

KEY FACT

Sometimes the answer to the previous question in a sequential question set is provided to you once you lock your answer. Do not be disheartened if you got it wrong. Simply understand that you now have an opportunity to get at least one answer correct in the sequence.

During the time allotted for each block in the USMLE Step 2 CK exam, you can answer test questions in any order and can also review responses and change your answers (except for responses within the sequential item sets described earlier). However, under no circumstances can you return to previous blocks and change your answers. Once you have finished a block, you must click on a screen icon to continue to the next block. Time not used during a testing block will be added to your overall break time (45 minutes total at start of exam), but it cannot be used to complete other testing blocks. Also note that a short tutorial (shorter than the one available at the USMLE website) is present at the start of the exam, which if you choose to skip, can add 15 minutes to your total break time.

KEY FACT

Expect to spend up to 9 hours at the test center.

TESTING CONDITIONS: WHAT WILL THE CBT BE LIKE?

Even if you are familiar with CBT and the Prometric test centers, you should still access the latest practice software from the USMLE Web site (http://www.usmle.org) and try out prior to the examination.

For security reasons, you are not allowed to bring personal equipment (except those needed for medical reasons and soft-foam earplugs as detailed later) into the testing area—which means that writing implements, outerwear, watches (even analog), cellular telephones, and electronic paging devices are all prohibited. Food and beverages are prohibited as well. The proctor will assign you a small locker to store your belongings and any food you bring for the day. You will also be given two 8 cm × 11 cm laminated writing surfaces, pens, and erasers for note taking and for recording your test Candidate Identification Number (CIN). You must return these materials after the examination. Note that you are not allowed to write on these until you enter the CIN number in the computer. Testing centers are monitored by audio and video surveillance equipment, and minimum of 2 surveillance rounds by the exam monitor per hour. Each time you enter the testing room, you will have to undergo a screening process to ensure that you are not bringing in personal items.

You should become familiar with a typical question screen. A window to the left displays all the questions in the block and shows you the unanswered questions (marked with an “i”). Some questions will contain figures, color illustrations, audio, or video adjacent to the question. Although the contrast and brightness of the screen can be adjusted, there are no other ways to manipulate the picture (eg, zooming or panning). Larger images are accessed with an **“exhibit”** button. You can also call up a window displaying normal **lab values**. You may **mark** questions to review at a later time by clicking the check mark at the top of the screen. The annotation feature functions like the provided dry-erase sheets and allows you to jot down notes during the examination. Play with the **highlighting/strike-out** and annotation features with the vignettes and multiple answers.

You should also do a few practice blocks to determine which tools will help you process questions more efficiently and accurately. If you find that you are not using the marking, annotation, or highlighting tools, then **keyboard shortcuts** can be quicker than using a mouse. Headphones are provided for listening to audio and blocking outside noise. Alternatively, you can bring soft earplugs to block excess noise. These earplugs must be examined by Prometric staff before you can take them into the testing area.

KEY FACT

Keyboard shortcuts:

- A–E—Letter choices.
- Enter or space bar—Move to the next question.
- Esc—Exit pop-up Lab and Exhibit windows.
- Alt-T—Countdown and time-elapsed clocks for current session and overall test.

WHAT DOES THE CBT FORMAT MEAN FOR ME?

The CBT format is the same format as that used on the USMLE Step 1. If you are uncomfortable with this testing format, spend some time playing with a Windows-based system and pointing and clicking icons or buttons with a mouse.

The USMLE also offers students an opportunity to take a simulated test, or practice session, at a Prometric center. The session is divided into three 1-hour blocks of up to 50 questions each. The approximately 127 Step 2 CK sample test items that are available on the USMLE Web site (http://www.usmle.org) are the same as those used at CBT practice sessions. **No new items are presented.** The cost is about $75 for US and Canadian students but is higher for international students. Students receive a printed percent-correct score after completing the session. No explanations of questions are provided. You may register for a practice session online at http://www.usmle.org.

The National Board of Medical Examiners (NBME) provides another option for students to assess their Step 2 CK knowledge with the Comprehensive Clinical Science Self-Assessment (CCSSA) test. This test is available on the NBME Web site for $60, which will display at the end of the exam all of the questions that you answered incorrectly. The current versions of the test also have answer explanations. The content of the CCSSA items resembles that of the USMLE Step 2 CK. After you complete the CCSSA, you will be given a performance profile indicating your strengths and weaknesses. This feedback is intended for use as a study tool only and is not necessarily an indicator of Step 2 CK performance. For more information on the CCSSA examination, visit the NBME's Web site at http://www.nbme.org, and click on the link for "Students and Residents."

HOW DO I REGISTER TO TAKE THE EXAMINATION?

Information on the Step 2 CK exam's format, content, and registration requirements are found on the USMLE Web site. To register for the examination, students/graduates of accredited schools in the United States and Canada can apply online at the NBME Web site (http://www.nbme.org), whereas students/graduates of non-US/Canadian schools should apply through the Educational Commission for Foreign Medical Graduates (ECFMG) (https://iwa2.ecfmg.org). A printable version of the application is also available on these sites.

The preliminary registration process for the USMLE Step 2 CK exam is as follows:

- Complete a registration form and send your examination fees to the NBME (online) for students in US/Canada medical schools, and to the ECFMG (online) for international medical students. The fees payable are outlined in Table 1.1.

TABLE 1.1 **Exam Fees for the USMLE Step 2 CK**

	FEE PAYABLE TO NBME (US AND CANADA SCHOOLS ONLY)	FEE PAYABLE TO ECFMG (ALL OTHER SCHOOLS)
Exam fee	$645	$985
Scheduling charge	None	$210
Eligibility period extension	$70	$100
Changing testing region	$90	$90
Requesting exam recheck	$80	$80

- Select a 3-month block in which you wish to be tested (eg, June/July/August).
- Attach a passport-type photo to your completed application form.
- Complete a Certification of Identification and Authorization form. This form must be signed by an official at your medical school such as from the registrar's office (if you are a student) or a notary public (if you have graduated) to verify your identity. It is valid for 5 years, allowing you to use only your USMLE identification number for future transactions.
- Send your certified application form to the NBME for processing. Applications may be submitted more than 6 months before the test date, but examinees will not receive their scheduling permits until 6 months prior to the eligibility period.
- The NBME will process your application within 4–6 weeks and will send you a slip of paper that will serve as your scheduling permit.
- Once you have received your scheduling permit, decide when and where you would like to take the examination. For a list of Prometric locations nearest you, visit https://www.prometric.com.
- Call Prometric's toll-free number or visit https://www.prometric.com to arrange a time to take the examination.

The Step 2 CK is offered on a year-round basis except for the first 2 weeks in January. For the most up-to-date information on available testing days at your preferred testing location, refer to http://www.usmle.org.

The scheduling permit you receive from the NBME will contain the following important information:

- Your USMLE identification number.
- The eligibility period during which you may take the examination.
- Your "scheduling number," which you will need to make your examination appointment with Prometric.
- Your CIN, which you must enter at your Prometric workstation in order to access the examination.

Prometric has no access to the codes and will not be able to supply these numbers, so do not lose your permit! You will not be allowed to take the Step 2 CK unless you present your permit along with an unexpired, government-issued photo identification that contains your signature (eg, driver's license, passport). Make sure the name on your photo ID exactly matches the name that appears on your scheduling permit.

KEY FACT

Because the Step 2 CK examination is scheduled on a "first-come, first-served" basis, you should be sure to call Prometric as soon as you receive your scheduling permit.

WHAT IF I NEED TO RESCHEDULE THE EXAMINATION?

You can change your date and/or center within your 3-month period by contacting Prometric if space is available. When you reschedule, a fee may apply (Table 1.2).

TABLE 1.2 Rescheduling Fees Payable to Prometric for USMLE Step 2 CK (1 Jan, 2022)

RESCHEDULING TIME BEFORE EXAM DATE	FEES FOR THE US AND CANADA TESTING REGION	FEES FOR TESTING REGIONS OTHER THAN THE US AND CANADA
46 days or more	No fee	No fee
Between 31 and 45 days	$35	$35
Between 6 days and 30 days	$100	$100
Less than 5 days	$144	$369

If you need to reschedule outside your initial 3-month period, you can apply for a single 3-month extension (eg, April/May/June can be extended through July/August/September) after your eligibility period has begun. For other rescheduling needs, you must submit a new application along with another application fee.

WHAT ABOUT TIME?

Time is of special interest on the CBT examination. The following is a breakdown of the examination schedule:

Tutorial	15 minutes
1-hour question blocks (40 questions per block)	8 hours
Break time (includes time for lunch)	45 minutes
Total test time	9 hours

The computer will keep track of how much time has elapsed during the examination. However, the computer will show you only how much time you have remaining in a block. Therefore, it is up to you to determine if you are pacing yourself properly.

The computer will not warn you if you are spending more than the 45 minutes allotted for break time. The break time includes not only the usual concept of a break—when you leave the testing area—but also the time it takes for you to make the transition to the next block, such as entering your CIN or even taking a quick stretch. **If you do exceed the 45-minute break time, the time to complete the last block of the test will be reduced.** However, you can elect not to use all of your break time, or you can gain extra break time either by skipping the tutorial or by finishing a block ahead of the allotted time.

SECURITY MEASURES

Smile! The USMLE uses a check-in/check-out process that includes electronic capture of your fingerprints and photograph. Fingerprints from a finger on each hand will be used for this process. These measures are intended to increase security by preventing fraud, thereby safeguarding the integrity of the examination. These procedures also decrease the amount of time needed to check in and out of the examination throughout the day, thereby maximizing your break time. However, you still need to sign out and sign in with the Test Center Log when exiting and entering the testing area.

IF I LEAVE DURING THE EXAMINATION, WHAT HAPPENS TO MY SCORE?

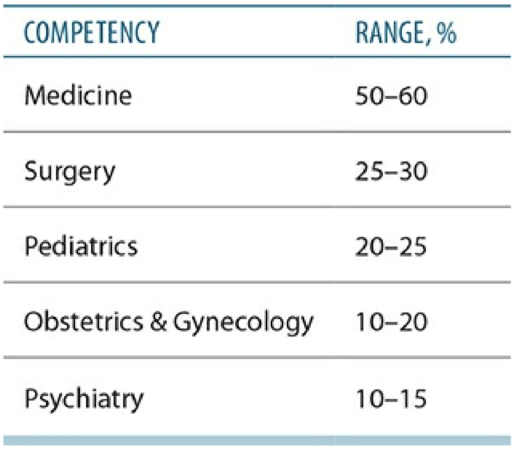
You are considered to have started the examination once you have entered your CIN onto the computer screen, but to receive an official score, you must finish the entire examination. This means that you must start and either finish or run out of time for each block of the examination. If you do not complete all of the question blocks, your examination will be documented on your USMLE score transcript as an incomplete attempt, but no actual score will be reported.

The examination ends when all blocks have been completed or time has expired. As you leave the testing center, you will receive a written test completion notice to document your completion of the examination.

WHAT TYPES OF QUESTIONS ARE ASKED?

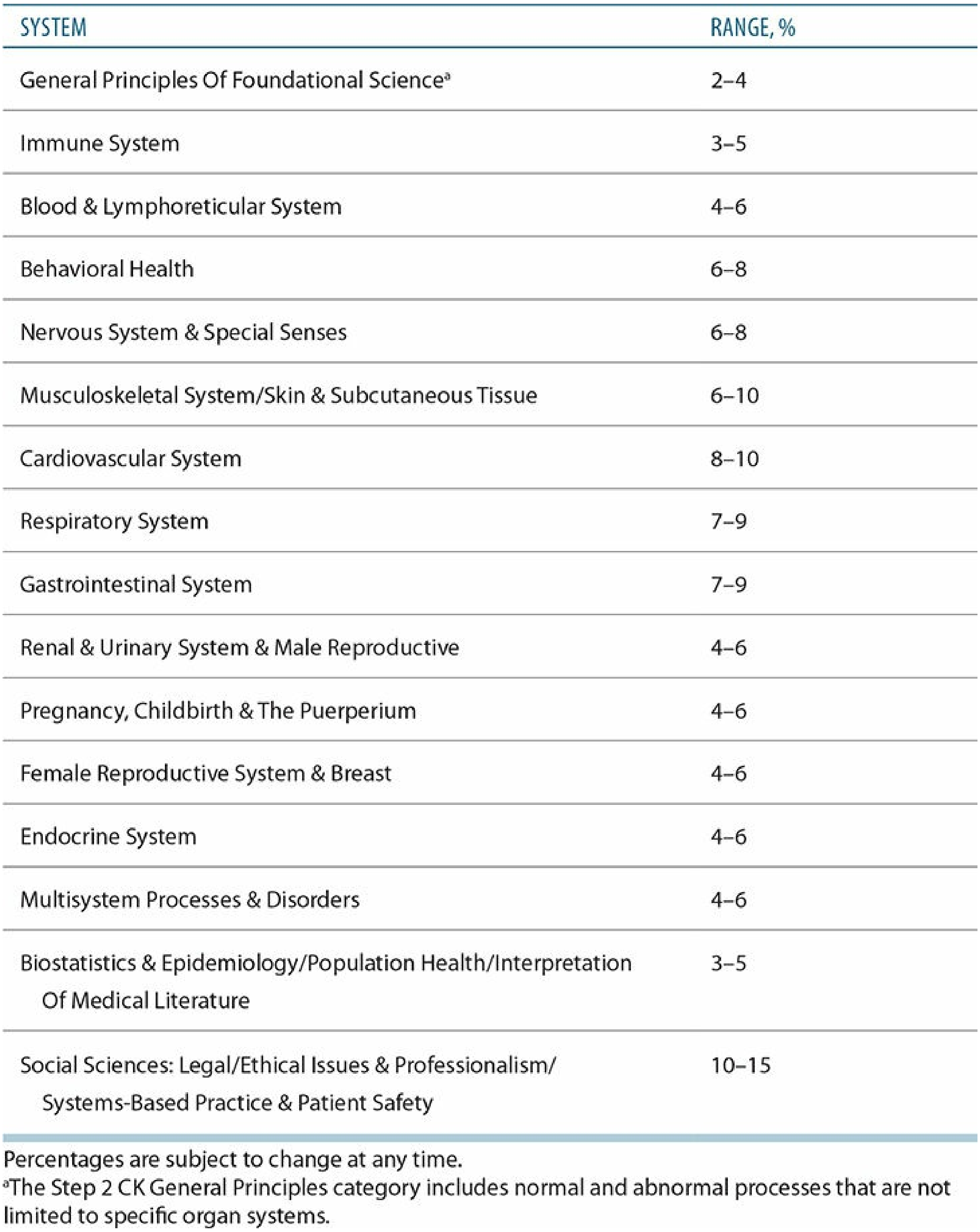
The Step 2 CK is an integrated examination that tests understanding of normal conditions, disease categories, and physician tasks. Almost all questions on the examination are case based. Some questions will involve interpreting a study or drug advertisement. A substantial amount of extraneous information may be given, or a clinical scenario may be followed by a question that could be answered without actually requiring that you read the case. It is your job to determine which information is superfluous and which is pertinent to the case at hand. Content areas include internal medicine, OB/GYN, pediatrics, preventive services, psychiatry, surgery, and other areas relevant to the provision of care under supervision (see Tables 1.3, 1.4, and 1.5).

TABLE 1.3 Exam Content Specification per Discipline



COMPETENCY	RANGE, %
Medicine	50–60
Surgery	25–30
Pediatrics	20–25
Obstetrics & Gynecology	10–20
Psychiatry	10–15

TABLE 1.4 **Exam Content Specification per System**

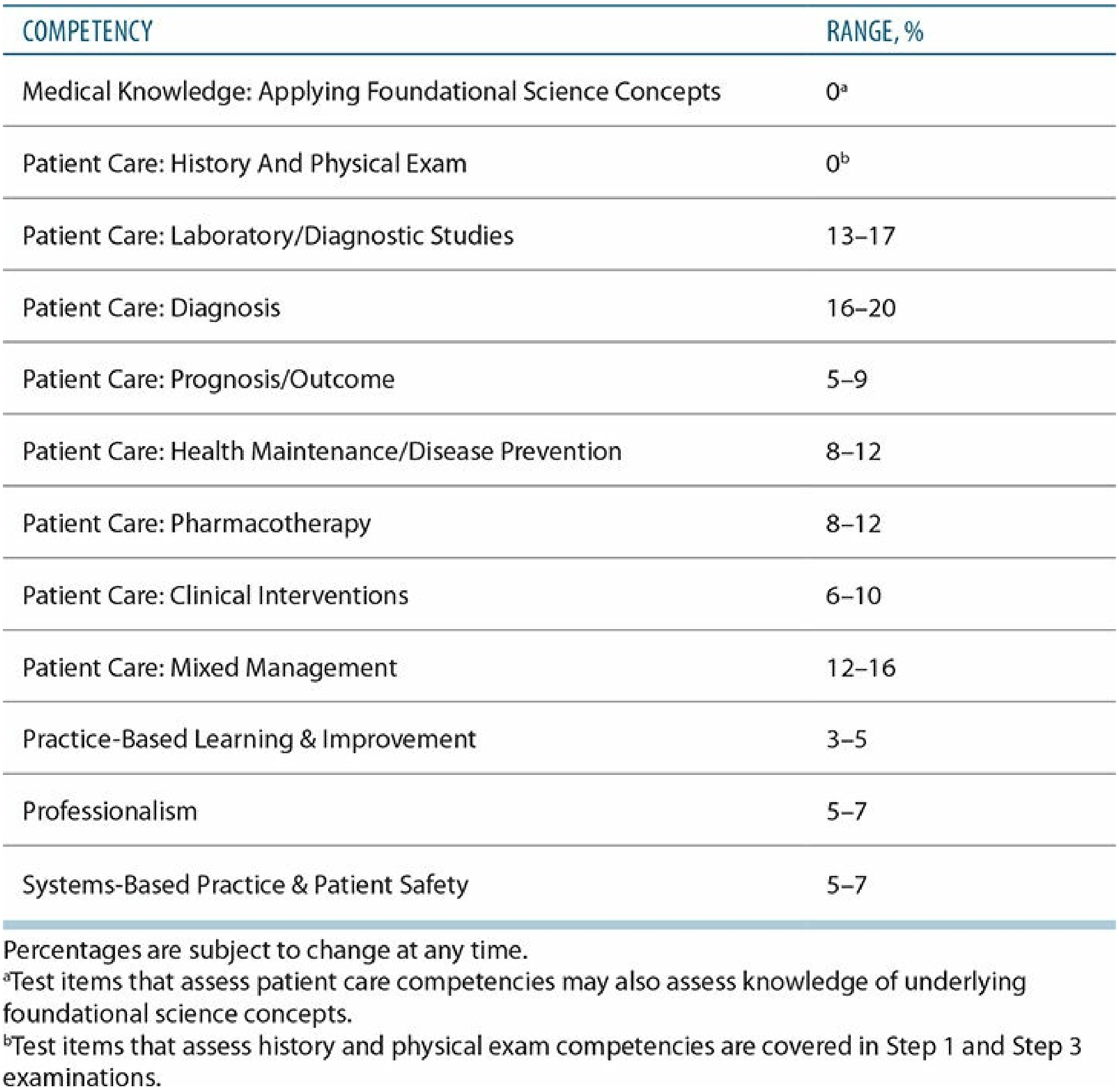


SYSTEM	RANGE, %
General Principles Of Foundational Science[a]	2–4
Immune System	3–5
Blood & Lymphoreticular System	4–6
Behavioral Health	6–8
Nervous System & Special Senses	6–8
Musculoskeletal System/Skin & Subcutaneous Tissue	6–10
Cardiovascular System	8–10
Respiratory System	7–9
Gastrointestinal System	7–9
Renal & Urinary System & Male Reproductive	4–6
Pregnancy, Childbirth & The Puerperium	4–6
Female Reproductive System & Breast	4–6
Endocrine System	4–6
Multisystem Processes & Disorders	4–6
Biostatistics & Epidemiology/Population Health/Interpretation Of Medical Literature	3–5
Social Sciences: Legal/Ethical Issues & Professionalism/ Systems-Based Practice & Patient Safety	10–15

Percentages are subject to change at any time.

[a] The Step 2 CK General Principles category includes normal and abnormal processes that are not limited to specific organ systems.

TABLE 1.5 Exam Content Specification per Physician Tasks/Competencies



COMPETENCY	RANGE, %
Medical Knowledge: Applying Foundational Science Concepts	0[a]
Patient Care: History And Physical Exam	0[b]
Patient Care: Laboratory/Diagnostic Studies	13–17
Patient Care: Diagnosis	16–20
Patient Care: Prognosis/Outcome	5–9
Patient Care: Health Maintenance/Disease Prevention	8–12
Patient Care: Pharmacotherapy	8–12
Patient Care: Clinical Interventions	6–10
Patient Care: Mixed Management	12–16
Practice-Based Learning & Improvement	3–5
Professionalism	5–7
Systems-Based Practice & Patient Safety	5–7

Percentages are subject to change at any time.

[a] Test items that assess patient care competencies may also assess knowledge of underlying foundational science concepts.

[b] Test items that assess history and physical exam competencies are covered in Step 1 and Step 3 examinations.

Most questions on the examination have a **single best-answer** format. The part of the vignette that actually asks the question—the **stem**—is usually found at the end of the scenario and generally relates to the physician task. From student experience, there are a few stems that are consistently addressed throughout the examination:

- What is the most likely diagnosis? (40%)
- Which of the following is the most appropriate initial step in management? (20%)
- Which of the following is the most appropriate next step in management? (20%)
- Which of the following is the most likely cause of…? (5%)
- Which of the following is the most likely pathogen…? (3%)
- Which of the following would most likely prevent…? (2%)
- Other (10%)

Additional examination tips are as follows:

- Note the age and race of the patient in each clinical scenario. When ethnicity is given, it is often relevant. Know these well (see high-yield facts), especially for more common diagnoses.

- Be able to recognize key facts that distinguish major diagnoses.
- Questions often describe clinical findings rather than naming eponyms (eg, they cite “audible hip click” instead of “positive Ortolani sign”).
- Questions about acute patient management (eg, trauma) in an emergency setting are common.

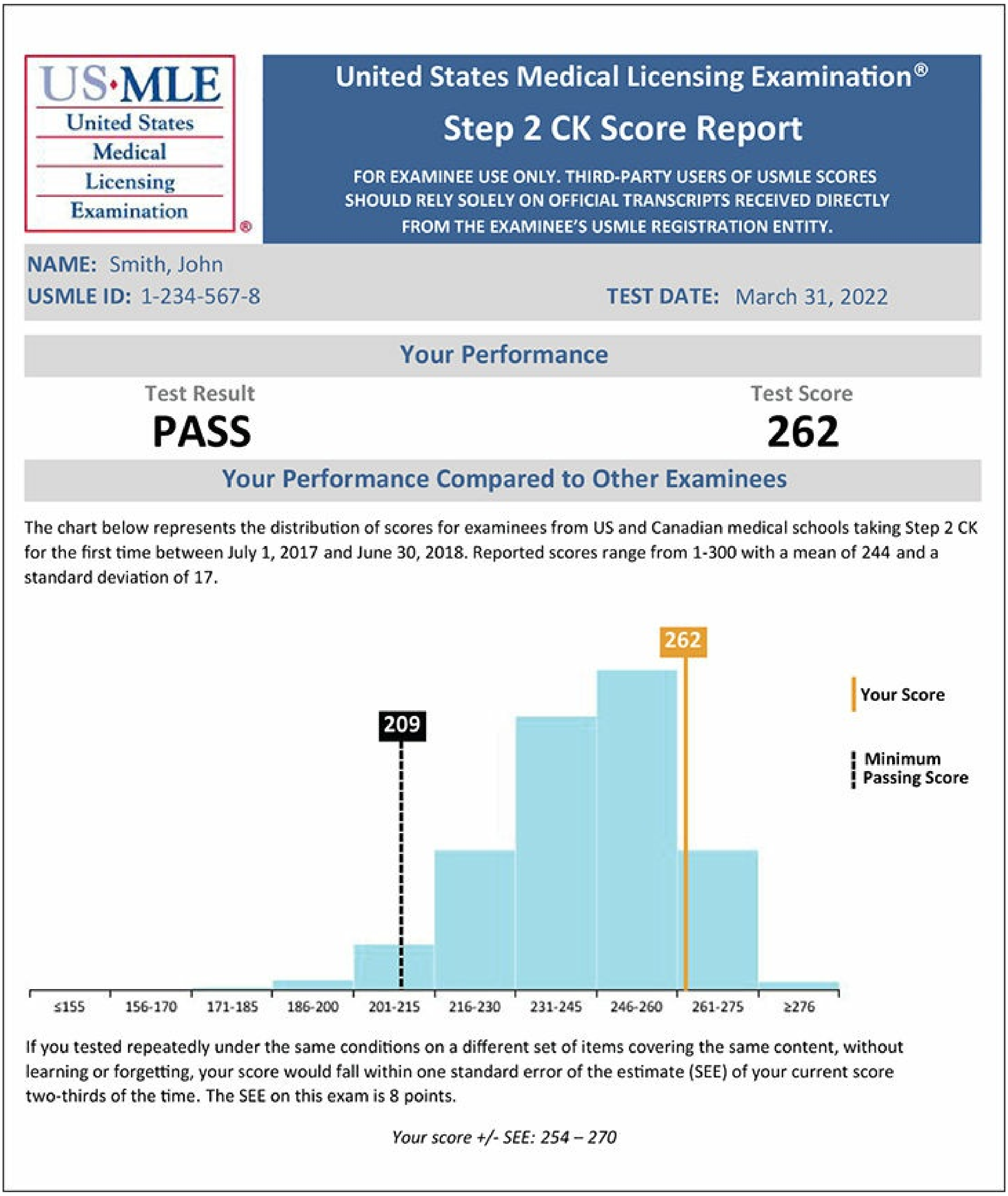
The cruel reality of the Step 2 CK examination is that no matter how much you study, there will still be questions you will not be able to answer with confidence. If you recognize that a question cannot be solved in a reasonable amount of time, make an educated guess and move on; you will not be penalized for guessing. Also bear in mind that some of the USMLE questions are “experimental” and will not count toward your score.

HOW LONG WILL I HAVE TO WAIT BEFORE I GET MY SCORES?

The USMLE reports scores 3–4 weeks after the examinee’s test date. During peak periods, however, as many as 6 weeks may pass before reports are scored. This usually includes scheduled delays after the first two weeks of the year in January when the scores may get delayed up to March. Official information concerning the time required for score reporting is posted on the USMLE Web site, http://www.usmle.org and recent changes may need to be checked every testing session.

HOW ARE THE SCORES REPORTED?

Like the Step 1 score report, your Step 2 CK report includes your pass/fail status, a numeric score, and a performance profile organized by discipline and disease process (see Fig. 1.1). The score is a 3-digit scaled score based on a predefined proficiency standard. The current required passing score is **214**. This score requires answering 60–70% of questions correctly. Any adjustments in the required passing score will be available on the USMLE Web site.



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Step 2 CK Score Report

FOR EXAMINEE USE ONLY. THIRD-PARTY USERS OF USMLE SCORES SHOULD RELY SOLELY ON OFFICIAL TRANSCRIPTS RECEIVED DIRECTLY FROM THE EXAMINEE'S USMLE REGISTRATION ENTITY.

NAME: Smith, John
USMLE ID: 1-234-567-8
TEST DATE: March 31, 2022

Your Performance

Test Result	Test Score
PASS	**262**

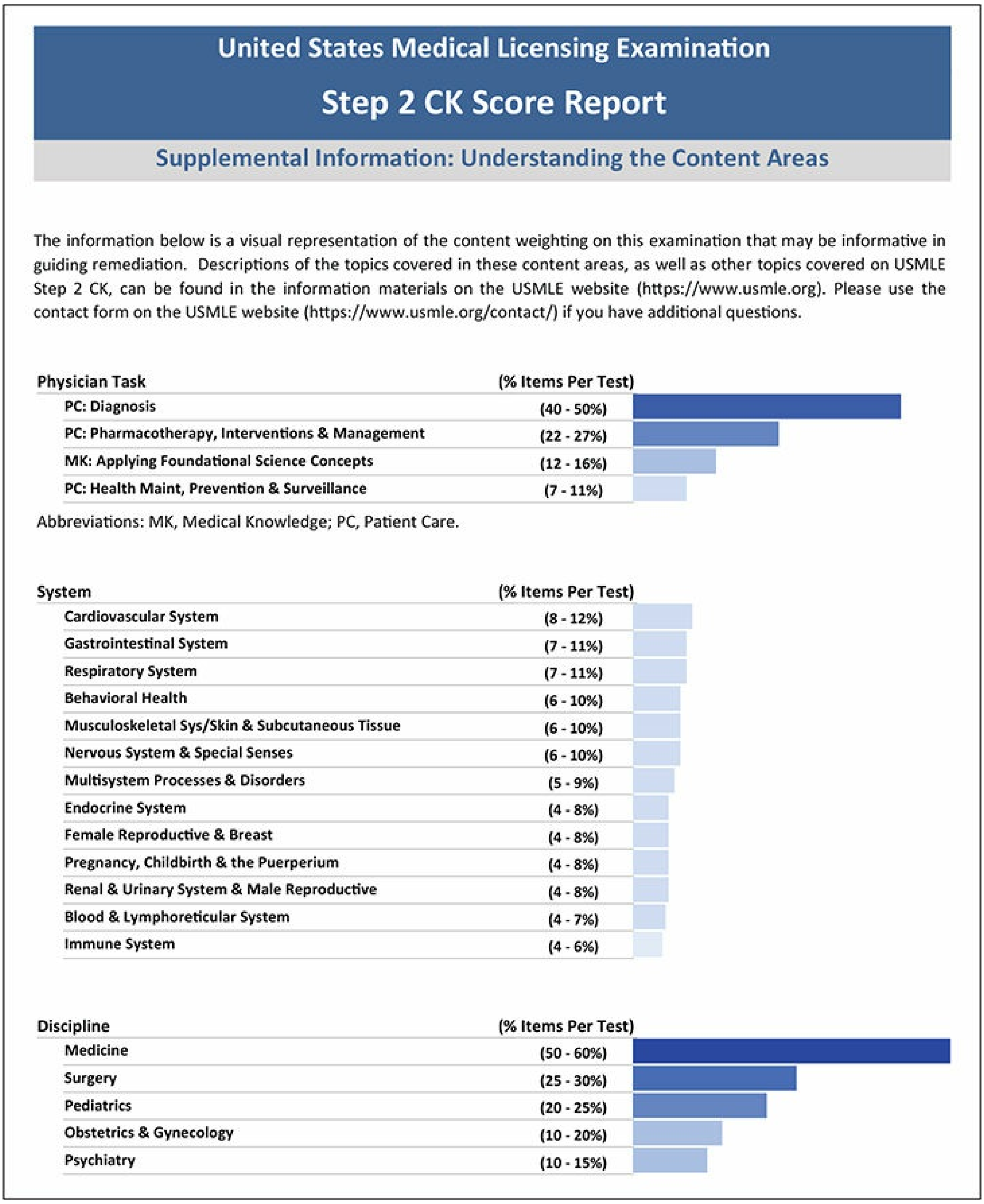
Your Performance Compared to Other Examinees

The chart below represents the distribution of scores for examinees from US and Canadian medical schools taking Step 2 CK for the first time between July 1, 2017 and June 30, 2018. Reported scores range from 1-300 with a mean of 244 and a standard deviation of 17.

If you tested repeatedly under the same conditions on a different set of items covering the same content, without learning or forgetting, your score would fall within one standard error of the estimate (SEE) of your current score two-thirds of the time. The SEE on this exam is 8 points.

Your score +/- SEE: 254 – 270

FIGURE 1-1. Sample score report—front page.



United States Medical Licensing Examination

Step 2 CK Score Report

Supplemental Information: Understanding the Content Areas

The information below is a visual representation of the content weighting on this examination that may be informative in guiding remediation. Descriptions of the topics covered in these content areas, as well as other topics covered on USMLE Step 2 CK, can be found in the information materials on the USMLE website (https://www.usmle.org). Please use the contact form on the USMLE website (https://www.usmle.org/contact/) if you have additional questions.

Physician Task	(% Items Per Test)
PC: Diagnosis	(40 - 50%)
PC: Pharmacotherapy, Interventions & Management	(22 - 27%)
MK: Applying Foundational Science Concepts	(12 - 16%)
PC: Health Maint, Prevention & Surveillance	(7 - 11%)

Abbreviations: MK, Medical Knowledge; PC, Patient Care.

System	(% Items Per Test)
Cardiovascular System	(8 - 12%)
Gastrointestinal System	(7 - 11%)
Respiratory System	(7 - 11%)
Behavioral Health	(6 - 10%)
Musculoskeletal Sys/Skin & Subcutaneous Tissue	(6 - 10%)
Nervous System & Special Senses	(6 - 10%)
Multisystem Processes & Disorders	(5 - 9%)
Endocrine System	(4 - 8%)
Female Reproductive & Breast	(4 - 8%)
Pregnancy, Childbirth & the Puerperium	(4 - 8%)
Renal & Urinary System & Male Reproductive	(4 - 8%)
Blood & Lymphoreticular System	(4 - 7%)
Immune System	(4 - 6%)

Discipline	(% Items Per Test)
Medicine	(50 - 60%)
Surgery	(25 - 30%)
Pediatrics	(20 - 25%)
Obstetrics & Gynecology	(10 - 20%)
Psychiatry	(10 - 15%)

FIGURE 1-1. Sample score report—back page.

DEFINING YOUR GOAL

Step 2 CK scores are becoming increasingly used for residency selection. The amount of time spent in preparation for this examination varies widely among medical students. Possible goals include the following:

- **Beating the mean.** This signifies an ability to integrate your clinical and factual knowledge to an extent that is superior to that of your peers (around 247 for recent examination administrations). Others redefine this goal as achieving a score 1 standard deviation above the mean (usually in the range of 250–260). Highly competitive residency programs may use your Step 1 and Step 2 scores (if available) as a screening tool or as a selection requirement. International medical graduates should aim to beat the mean, as USMLE scores are likely to be a selection factor even for less competitive US residency programs.

- **Acing the exam.** Perhaps you are one of those individuals for whom nothing less than the best will do—and for whom excelling on standardized examinations is a source of pride and satisfaction.
- **Evaluating your clinical knowledge.** In many ways, this goal should serve as the ultimate rationale for taking the Step 2 CK, as it is technically the reason the examination was initially designed. The case-based nature of the Step 2 CK differs significantly from the more fact-based Step 1 examination in that it more thoroughly assesses your ability to recognize classic clinical presentations, deal with emergent situations, and follow the step-by-step thought processes involved in the treatment of particular diseases.
- **Preparing for internship.** Studying for the USMLE Step 2 CK is an excellent way to review and consolidate all of the information you have learned in preparation for internship.

Matching statistics, including examination scores related to various specialties, are available at the National Resident Matching Program Web site at https://www.nrmp.org under "Data and Reports."

WHEN TO TAKE THE EXAM

The second most important thing to do in your exam preparation is to decide when to take the examination. With the CBT, you now have a wide variety of options regarding when to take the Step 2 CK. Here are a few factors to consider:

- **The nature of your objectives,** as defined earlier.
- **The specialty to which you are applying.** An increasing number of residency programs are viewing the Step 2 CK as an integral part of the residency application process. Several research publications demonstrate the increasing importance placed on this examination by residency directors. Some programs are now requiring the Step 2 CK score in order to rank candidates for a residency position. It is therefore in the best interest of candidates to have this examination done in time for scores to be available for the residency application. Taking the examination in June or July ensures that scores will be available for the Match period that begins in September. Some programs, however, will accept scores after the application process starts. Check with programs in your desired specialty to determine when to take the exam.
- **Prerequisite to graduation.** If passing the USMLE Step 2 CK is a prerequisite to graduation at your medical school, you will need to take the examination in the fall or winter at the latest.
- **Proximity to clerkships.** Many students feel that the core clerkship material is fresher in their minds early in the fourth year, making a good argument for taking the Step 2 CK earlier in the fall.
- **The nature of your schedule.**
- **Considerations for MD/PhD students.** The dates of passing the Step 1, Step 2, and Step 3 examinations should occur within a 7-year period. However, the typical pathway for MD/PhD students consists of 2–3 years of preclinical (and sometimes clinical) work in

medical school, 3–4 years of graduate work with research, and finally returning to medical school for clinical work. MD/PhD students typically exceed the 7-year limit. Depending on the state in which licensure is sought, such students may need to petition their licensure body for an exception to this rule.

- **Considerations for International Medical Graduates.** A passing score on the Step 2 CK is required to qualify for ECFMG certification which is necessary to match. It is generally recommended to take the Step 2 CK early enough to obtain ECFMG certification before interview season is completed, ideally even before applications are reviewed by programs.

KEY FACT

The Step 2 CK is an opportunity to consolidate your clinical knowledge and prepare for internship.

HOW WILL THE STEP 2 CK SCORE AFFECT MY MATCH?

Since Step 1 is now being reported as pass or fail, it is expected that the Step 2 CK score may take on more importance. Programs receive hundreds if not thousands of applications yearly, and they rely on certain objective metrics to select applicants to interview. Having a competitive Step 2 CK score will not guarantee a match at a top choice program but it will strengthen your application. It is one of many elements that programs will consider.

STUDY RESOURCES

QUALITY CONSIDERATIONS

Although an ever-increasing number of USMLE Step 2 CK review books and software packages are available on the market, the quality of these materials is highly variable (see Section 3). Some common problems include the following:

- Some review books are too detailed to be reviewed in a reasonable amount of time or cover subtopics that are not emphasized on the examination (eg, a 400-page anesthesiology book).
- Many sample question books have not been updated to reflect current trends on the Step 2 CK.
- Many sample question books use poorly written questions, contain factual errors in their explanations, give overly detailed explanations, or offer no explanations at all.
- Software for boards review is of highly variable quality, may be difficult to install, and may be fraught with bugs.

CLINICAL REVIEW BOOKS

Many review books are available, so you must decide which ones to buy by carefully evaluating their relative merits. Toward this goal, you should compare different opinions from other medical students; read the reviews and ratings in Section 3 of this guide, and examine the various books closely in the bookstore. Do not worry about finding the "perfect" book, as many subjects simply do not have one.

KEY FACT

The best review book for you reflects the way you like to learn. If a given review book is not working for you, stop using it no matter how highly rated it may be.

There are two types of review books: those that are stand-alone titles and those that are part of a series. Books in a series generally have the same style, and you must decide if that style is helpful for you and optimal for a given subject.

TEST BANKS

A test bank can serve multiple functions, including the following:

- Provide information about strengths and weaknesses in your fund of knowledge.
- Add variety to your study schedule.
- Serve as the main form of study.
- Improve test-taking skills.
- Familiarize examinees with the style of the USMLE Step 2 CK examination.

Students report that some test banks have questions that are, on average, shorter and less clinically oriented than those on the current Step 2 CK exam. Step 2 CK questions demand fast reading skills and the application of clinical facts in a problem-solving format. Approach sample examinations critically, and do not waste time with low-quality test bank questions until you have exhausted better sources.

KEY FACT

Use test banks to identify concepts and areas of weakness, not just facts that you missed.

After you have taken a practice test, try to identify concepts and areas of weakness, not just the facts that you missed. Use this experience to motivate your study and to prioritize the areas in which you need the most work. Analyze the pattern of your responses to questions to determine if you have made systematic errors in answering questions. Common mistakes include reading too much into the question, second-guessing your initial impression, and misinterpreting the question.

TEXTS AND NOTES

Most textbooks are too detailed for high-yield boards review and should be avoided. When using texts or notes, engage in active learning by making tables, diagrams, new mnemonics, and conceptual associations whenever possible. If you already have your own mnemonics, do not bother trying to memorize someone else’s. Textbooks are useful; however, they are best used to supplement incomplete or unclear material.

COMMERCIAL COURSES

Commercial preparation courses can be helpful for some students, as they offer an effective way to organize study material. However, multiweek courses are costly and require significant time commitment, leaving limited time for independent study. Also note that some commercial courses are designed for first-time test takers, students who are repeating the examination, or international medical graduates.

NBME/USMLE PUBLICATIONS

We strongly encourage students to use the free materials provided by the testing agencies and to study the following NBME publications:

- ***USMLE Step 2 Clinical Knowledge (CK): Content Description and General Information.*** This publication provides you with nuts-and-bolts details about the examination (included on the Web site http://www.usmle.org; free to all examinees).
- ***USMLE Step 2 Clinical Knowledge (CK): Sample Test Questions.*** This is a PDF version of the test questions and test content also found at http://www.usmle.org under “Prepare for your exam”.
- **USMLE Web site** (http://www.usmle.org). In addition to allowing you to become familiar with the CBT format, the sample items on the USMLE Web site provide the only questions that are available directly from the test makers. Student feedback varies as to the similarity of these questions to those on the actual exam, but they are nonetheless worthwhile to know.

TEST-DAY CHECKLIST

THINGS TO BRING WITH YOU TO THE EXAM

- Be sure to bring your scheduling permit as a hard copy and a photo ID with signature. (You will not be admitted to the examination if you fail to bring your permit, and Prometric will charge a rescheduling fee.)
- Remember to bring lunch, snacks (for a little “sugar rush” on breaks), and fluids (including a caffeine-containing drink if needed).
- Bring clothes to layer to accommodate temperature variations at the testing center.
- Earplugs will be provided at the Prometric center.
- Remove all jewelry (eg, earrings, necklaces) before entering the testing center.
- Bring acetaminophen/ibuprofen, in case you develop a headache during the exam.
- Check the USMLE Web site (http://www.usmle.org/test-accommodations/PIEs.html) for the personal item exception list to see if a medical device or personal item that you need is allowed into the testing facility without submitting a special request.
  - If you have a medical condition that requires use of an item NOT on the above list, contact the NBME personal item exception (PIE) coordinator at disabilityservices@NBME.org or (215) 590-9700 for additional information on how to request a personal item exception.
- If you need test accommodation for one of the following reasons: assistance with keyboard tasks, audio rendition, extended testing time, additional break time, you need to fill in a request by going to the website https://www.usmle.org/step-exams/test-accommodations

TESTING AGENCIES

National Board of Medical Examiners (NBME)
Department of Licensing Examination Services
3750 Market Street
Philadelphia, PA 19104-3102
Customer Service: (215) 590-9700, Front Desk: (215) 590-9500
Fax: (215) 590-9460
http://www.nbme.org/contact/
e-mail: webmail@nbme.org

USMLE Secretariat
3750 Market Street
Philadelphia, PA 19104-3190
(215) 590-9700
Fax: (215) 590-9460
http://www.usmle.org
e-mail: webmail@nbme.org

Educational Commission for Foreign Medical Graduates (ECFMG)
3624 Market Street
Philadelphia, PA 19104-2685
(215) 386-5900
Fax: (215) 386-9196
http://www.ecfmg.org/contact.html
e-mail: info@ecfmg.org

Federation of State Medical Boards (FSMB)
400 Fuller Wiser Road, Suite 300
Euless, TX 76039
(817) 868-4041
Fax: (817) 868-4098
http://www.fsmb.org/contact-us
e-mail: usmle@fsmb.org

SECTION 2

DATABASE OF HIGH-YIELD FACTS

Cardiovascular

Dermatology

Endocrinology

Epidemiology

Health Systems Science

Gastrointestinal

Hematology

Musculoskeletal

Neurology

Obstetrics

Gynecology

Pediatrics

Psychiatry

Pulmonary

Renal/Genitourinary

Multisystem

Rapid Review

HOW TO USE THE DATABASE

The 11th edition of *First Aid for the USMLE Step 2 CK* contains a revised and expanded database of clinical material that student authors and faculty have identified as high yield for boards review. We have organized information according to subject matter, whether medical specialty (eg, Cardiovascular, Renal) or high-yield topic (eg, Health Systems Science). Each subject then branches out into smaller subsections of related facts.

Individual facts appear in a logical fashion, from basic definitions and epidemiology to history/physical exam, diagnosis, and treatment. Lists, mnemonics, pull quotes, vignette flash cards, and tables help the reader form key associations. In addition, we have interspersed color and black-and-white photos throughout the text. At the end of Section 2, we also feature a Rapid Review chapter consisting of key facts and classic associations that can be studied a day or two before the exam.

The content contained herein is useful primarily for the purpose of reviewing material already learned. The information presented is not ideal for learning complex or highly conceptual material for the first time.

The Database of High-Yield Facts is not meant to be comprehensive. Use it to complement your core study material, not as your primary study source. We have condensed and edited the facts and notes to emphasize essential material. Work with the material, add your own notes and mnemonics, and recognize that not all memory techniques work for all students.

We update material to keep current with new trends in boards content, as well as to expand our database of high-yield information. However, we must note that our database inevitably does not include many other high-yield entries and topics.

We actively encourage medical students and faculty to submit entries and mnemonics so that we may enhance the database for future students. We also solicit recommendations for additional study tools that may be useful in preparing for the exam, such as diagrams, charts, and computer-based tutorials (see How to Contribute, p. xi).

DISCLAIMER

The entries in this section reflect student opinions of what is high yield. Owing to the diverse sources of material, we have made no attempt to trace or reference origins of individual entries. We have regarded mnemonics as essentially in the public domain. We will gladly correct errors and omissions if brought to the attention of the authors, either through the publisher or directly by email.

HIGH-YIELD FACTS IN

CARDIOVASCULAR

Electrocardiogram

Cardiac Physical Exam

Arrhythmias
  BRADYARRHYTHMIAS AND CONDUCTION ABNORMALITIES
  TACHYARRHYTHMIAS

Cardiac Life Support Basics

Congestive Heart Failure
  CLASSIFICATION
  SYSTOLIC DYSFUNCTION/HEART FAILURE WITH REDUCED EJECTION FRACTION
  HEART FAILURE WITH PRESERVED EJECTION FRACTION

Cardiomyopathy
  DILATED CARDIOMYOPATHY
  HYPERTROPHIC CARDIOMYOPATHY
  ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA
  RESTRICTIVE CARDIOMYOPATHY
  SECONDARY CARDIOMYOPATHY
  OTHER CARDIOMYOPATHIES

Coronary Artery Disease
  ANGINA PECTORIS
  PRINZMETAL (VARIANT) ANGINA

Acute Coronary Syndromes
  UNSTABLE ANGINA/NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION
  ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION
  CAROTID ARTERY STENOSIS

Dyslipidemia

Hypertension
  PRIMARY (ESSENTIAL) HYPERTENSION
  SECONDARY HYPERTENSION
  HYPERTENSIVE EMERGENCY/URGENCY

Pericardial Disease
  ACUTE PERICARDITIS
  CONSTRICTIVE PERICARDITIS
  PERICARDIAL EFFUSION
  CARDIAC TAMPONADE

Endocarditis

Valvular Heart Disease

Vascular Diseases
- AORTIC ANEURYSM
- AORTIC DISSECTION
- DEEP VENOUS THROMBOSIS
- POSTTHROMBOTIC (POSTPHLEBITIC) SYNDROME
- PERIPHERAL ARTERIAL DISEASE
- LYMPHEDEMA

Syncope

ELECTROCARDIOGRAM

An ECG provides an assessment of the electrical activity of the heart. The heart rate, rhythm, axis, intervals, ischemia, and chamber enlargement can be evaluated (Fig. 2.1-1).

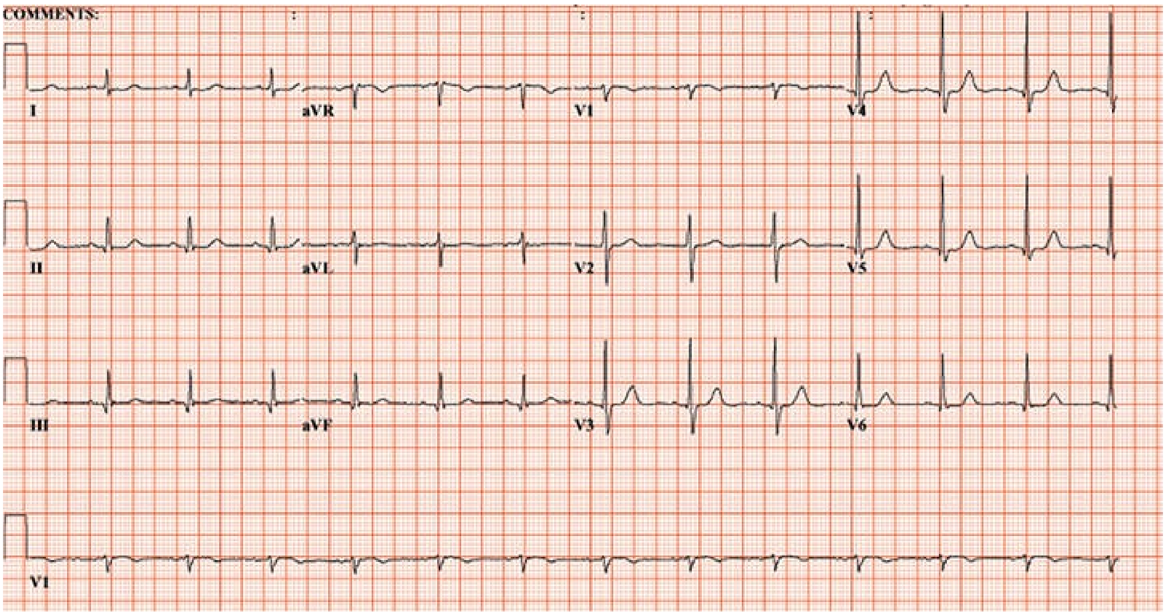


FIGURE 2.1-1. Normal electrocardiogram from a healthy subject. (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

*Heart rate = 300/number of large boxes between two consecutive QRS complexes.
*Presuming ECG recorded at usual speed (25 mm/sec), where each large box = 200 msec and each small box = 40 msec.

Rate

Normal adult heart rate (HR) is 60–100 beats/min (bpm). HR <60 bpm is bradycardia. Heart rate >100 bpm is tachycardia. Common causes of sinus bradycardia are physical fitness, sick sinus syndrome, drugs, vasovagal attacks, acute myocardial infarction (MI), and ↑ intracranial pressure. Common causes of sinus tachycardia are anxiety, anemia, pain, fever, sepsis, congestive heart failure (CHF), pulmonary embolism, hypovolemia, thyrotoxicosis, carbon dioxide (CO_2) retention, and sympathomimetics.

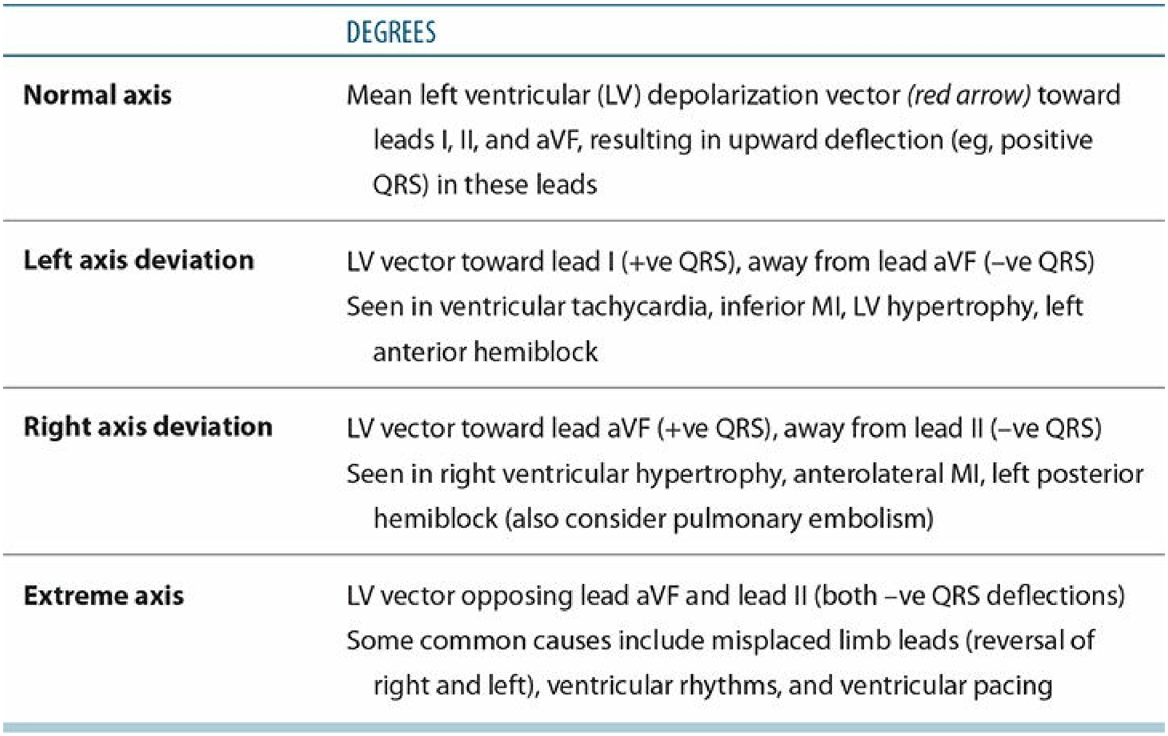
Rhythm

Sinus rhythm: Normal rhythm that originates from the sinus node. It is characterized by a P wave (upright in leads II, III, and aVF; inverted in lead aVR) preceding every QRS complex and a QRS complex following every P wave. Sinus arrhythmia is a sinus rhythm originating from the sinoatrial (SA) node with cyclical beat-to-beat variation (>120 milliseconds [msec]) in the P-P interval and a constant P-R interval, which results in an irregular ventricular rate. It is common in young adults and is considered a normal variant.

Axis

The QRS axis represents the direction in which the mean QRS current flows. It can be determined by examining the QRS in leads I, II, and aVF (see Table 2.1-1 and Fig. 2.1-2).

TABLE 2.1-1. Axis Deviation by ECG Findings



	DEGREES
Normal axis	Mean left ventricular (LV) depolarization vector *(red arrow)* toward leads I, II, and aVF, resulting in upward deflection (eg, positive QRS) in these leads
Left axis deviation	LV vector toward lead I (+ve QRS), away from lead aVF (–ve QRS) Seen in ventricular tachycardia, inferior MI, LV hypertrophy, left anterior hemiblock
Right axis deviation	LV vector toward lead aVF (+ve QRS), away from lead II (–ve QRS) Seen in right ventricular hypertrophy, anterolateral MI, left posterior hemiblock (also consider pulmonary embolism)
Extreme axis	LV vector opposing lead aVF and lead II (both –ve QRS deflections) Some common causes include misplaced limb leads (reversal of right and left), ventricular rhythms, and ventricular pacing

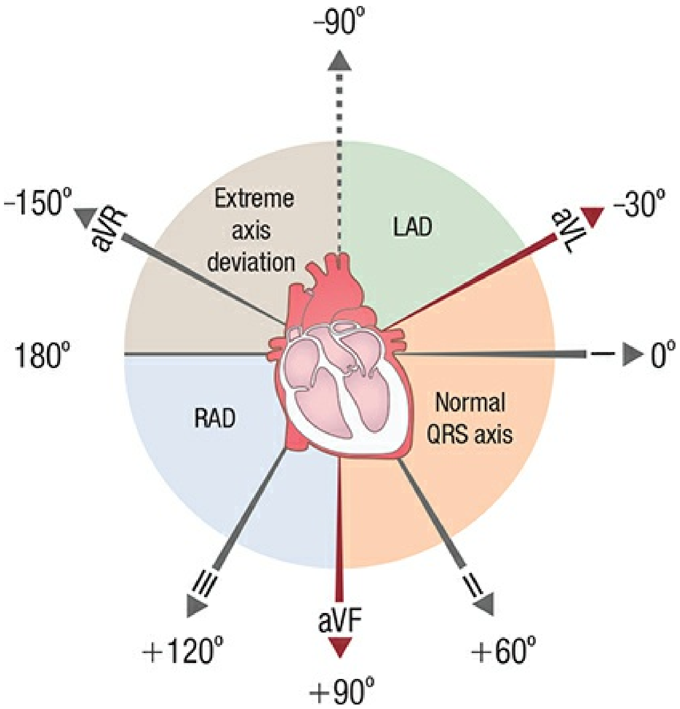


FIGURE 2.1-2. **ECG axis interpretation.** QRS axis and frontal leads. (Reproduced with permission from USMLE-Rx.com.)

Intervals

- **PR interval:** Normally 120 to 200 msec (3–5 small boxes).
  - Prolonged = delayed atrioventricular (AV) conduction (eg, first-degree heart block).
  - Short = fast AV conduction down accessory pathway (eg, Wolff-Parkinson-White [WPW] syndrome).
- **QRS interval:** Normally <120 msec. A normal Q wave is <40 msec wide and <2 mm deep. Ventricular conduction defects can cause a widened QRS complex (>120 msec):
  - **Left bundle-branch block (LBBB):** Deep S wave and no R wave in V_1 ("W" shaped); wide, tall and broad, or notched ("M"-shaped) R waves in I, V_5, and V_6 (Fig. 2.1-3). A new LBBB is pathologic, and it may be suggestive of acute MI. However, this is not diagnostic in isolation. Rather, the Modified Sgarbossa Criteria (see key fact) should be used for the ECG diagnosis of acute MI in this situation (higher sensitivity and specificity).

KEY FACT

Smith-Modified Sgarbossa Criteria are used to diagnose MI in the presence of LBBB should be suspected in a patient with LBBB and the following ECG findings:

- Concordant ST elevation (STE) ≥1 mm in ≥1 lead
- Concordant ST depression ≥1 mm in ≥1 lead of V_1–V_3
- Excessive discordant STE in ≥1 lead with ≥1 mm STE, where excessive discordance is defined as STE to the maximum QRS amplitude ratio ≥25%

  - **Right bundle-branch block (RBBB):** RSR′ complex ("rabbit ears;" "M"-shaped); qR or R morphology with a wide R wave in V_1; QRS pattern with a wide S wave in I, V_5, and V_6 (see Fig. 2.1-3).

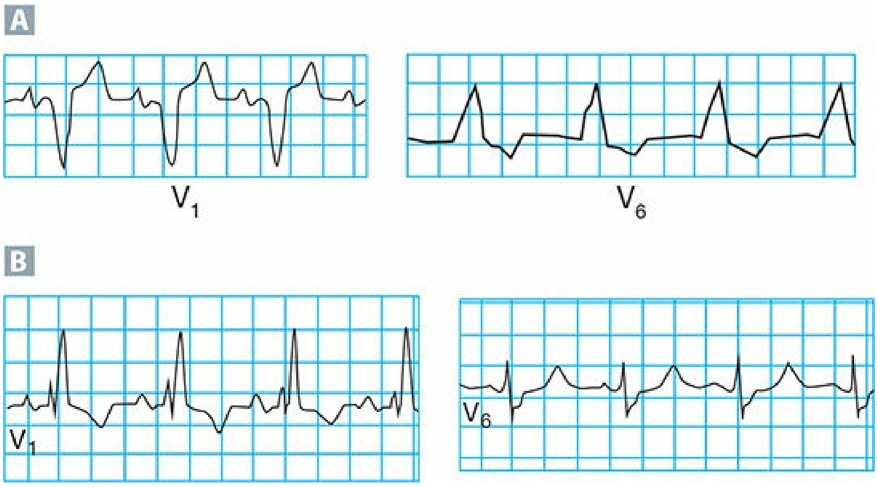

A
V1
V6
B
V1
V6

FIGURE 2.1-3. **Bundle branch block.** Characteristic ECG findings in left bundle branch block **(A)** and right bundle branch block **(B)** are seen in leads V_1 and V_6. (Modified with permission from USMLE-Rx.com.)

- **QT interval:** Normally QTc (the QT interval corrected for extremes in heart rate) is 380 to 440 msec (QTc = QT/√RR). QTc may be prolonged (QTc >440 msec) due to acquired causes, including electrolyte derangements (↓ K^+, ↓ Ca^{2+}, ↓ Mg^{2+}) and medications (macrolides, fluroquinolones, opioids, ondansetron, Classes Ia [quinidine, procainamide] and III [sotalol, amiodarone] antiarrhythmic drugs). Congenital causes include long QT syndrome (LQTS), an underdiagnosed disorder that predisposes to ventricular tachyarrhythmias (eg, torsade de pointes) and sudden cardiac death (SCD, see later).
  - **Romano Ward syndrome** is the most common congenital cause of LQTS with autosomal dominant inheritance. Presents as a purely cardiac phenotype (no deafness).
  - **Jervell and Lange-Nielsen syndrome** is an autosomal recessive cause of LQTS caused by a defect in K+ channel conduction. Most likely diagnosis in a child with sensorineural deafness, syncope on exercise, ventricular arrhythmias, and prolonged QT. Treat with β-blockers and implantable cardiac defibrillator (ICD) or pacemaker.

Ischemia/Infarction

Acute ischemia: See Figure 2.1-4 describing progression of ECG changes over time in ST-segment elevation MI (STEMI).

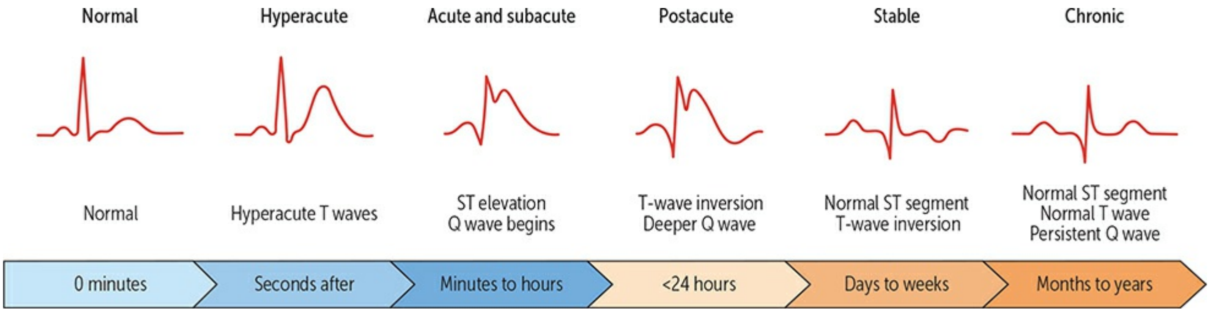

Normal
Hyperacute
Acute and subacute
Postacute
Stable
Chronic
Normal
Hyperacute T waves
ST elevation
Q wave begins
T-wave inversion
Deeper Q wave
Normal ST segment
T-wave inversion
Normal ST segment
Normal T wave
Persistent Q wave
0 minutes
Seconds after
Minutes to hours
<24 hours
Days to weeks
Months to years

FIGURE 2.1-4. **ECG changes in acute ST-elevation myocardial infarction (STEMI) over time.** (Reproduced with permission from USMLE-Rx.com.)

- Within hours, peaked T-waves and ST-segment changes (either depression or elevation).
- Within 24 hours, T-wave inversion and ST-segment resolution.
- Within a few days, pathologic Q waves (>40 msec or more than one-third of the QRS amplitude). Q waves usually persist, but may resolve in 10% of patients. Because of this,

Q waves signify either acute or prior ischemic events.

- Non–Q-wave infarcts (also known as subendocardial infarcts) have ST and T changes without Q waves.
- In a normal ECG, R waves increase in size compared to the S wave between leads V_1 and V_5. Poor R-wave progression refers to abnormalities in this pattern (eg, reversed progression [R in $V_2 > V_3$], transition point beyond V_4, R in V_3 <3 mm) and can be a sign of new or prior anterior infarction, although it is not specific.

MNEMONIC

Pulmonale causes **P**eaked P waves.
Mitrale causes **M**-shaped P waves.

Chamber Enlargement

Atrial enlargement:

- **Right atrial abnormality (P pulmonale):** Generally, the right atrium (RA) depolarizes before the left. Right atrial enlargement (due to pulmonary hypertension [eg, chronic obstructive, pulmonary disease, tetralogy of Fallot, tricuspid atresia]) causes slowed conduction; therefore peak right atrial depolarization coincides with left. This results in increased P-wave amplitude (>2.5 mm in lead II).
- **Left atrial abnormality (P mitrale):** Left atrial enlargement causes prolonged left atrial (LA) depolarization, increased P-wave duration (>120 msec in lead II), and sometimes a notched P wave (also in lead II). Also, the P wave in lead V_1 may have a large negative deflection (>1 small square wide and 1 small square deep in a standard tracing). Commonly seen in isolation in mitral stenosis or associated with LV hypertrophy.
- **Left ventricular hypertrophy (LVH, Fig. 2.1-5):**

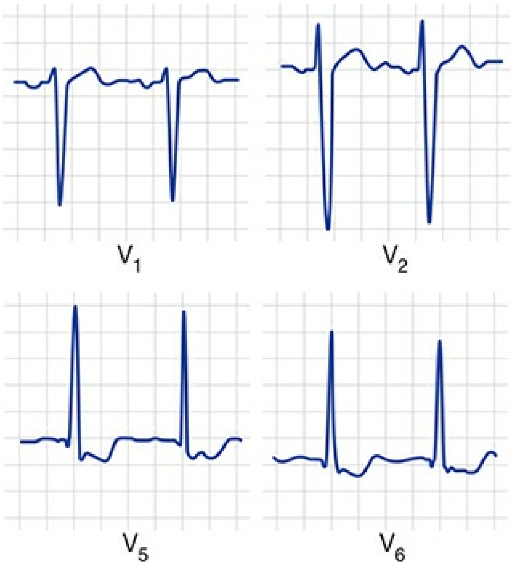


FIGURE 2.1-5. **Left ventricular hypertrophy.** Shown are leads V_1, V_2, V_5, and V_6. S wave in V_1 + R wave in V_5 = 45 mm. Note ST changes and T-wave inversion in V_5 and V_6, suggesting strain. (Reproduced with permission from USMLE-Rx.com.)

  - Amplitude of S in V_1 + R in V_5 or V_6 is >35 mm.
  - **Alternative criteria:** The amplitude of R in aVL + S in V_3 is >28 mm in men or >20 mm in women.
  - Usually associated with ST depression and T-wave changes.
  - Causes include hypertension (most common), aortic stenosis/regurgitation, mitral regurgitation, coarctation of the aorta, and hypertrophic cardiomyopathy.

KEY FACT

Axis deviation can be a sign of ventricular enlargement.

- **Right ventricular hypertrophy (RVH):**
  - Right-axis deviation and an R wave in V_1 >7 mm.
  - Causes include pulmonary hypertension, pulmonary embolism, chronic lung disease (cor pulmonale), mitral stenosis, and congenital heart disease (eg, tetralogy of Fallot, pulmonary stenosis).

MNEMONIC

"D ARMS PITS"

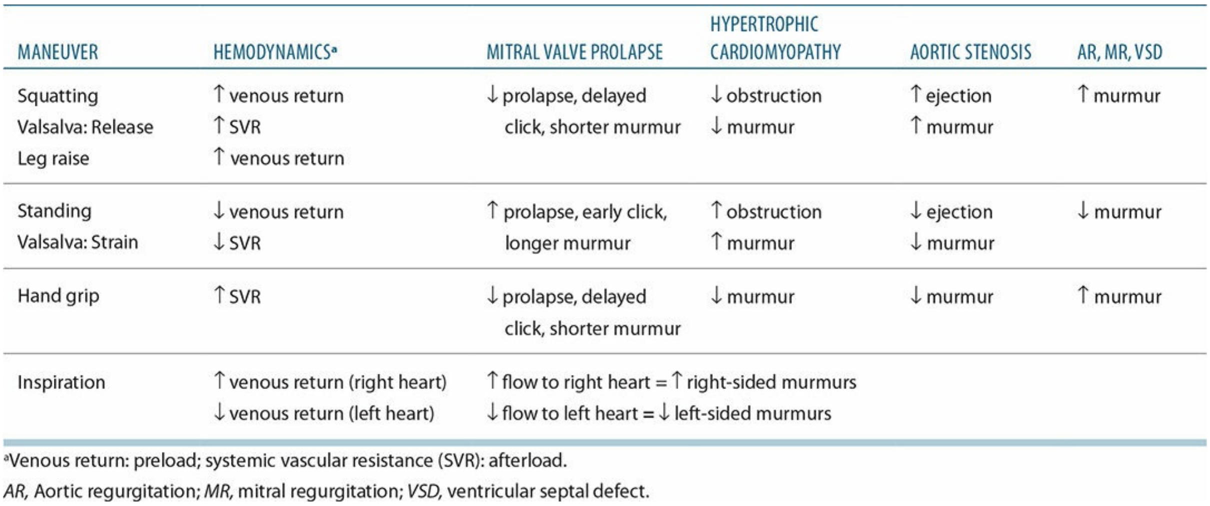
Diastolic **M**urmurs
Aortic **R**egurgitation
Mitral **S**tenosis
Pulmonary **I**nsufficiency
Tricuspid **S**tenosis

CARDIAC PHYSICAL EXAM

Key exam findings that can narrow the differential include the following:

- **Jugular venous distention (JVD):** >3 cm above the sternal angle when head of the bed is at 30 to 45 degrees of inclination. Most typically from volume overload, stemming from conditions such as right heart failure or pulmonary hypertension.
- **Hepatojugular reflux:** Distention of neck veins upon applying pressure to the liver. Seen in same conditions as JVD.
- **Kussmaul sign:** ↑ in jugular venous pressure (JVP) with inspiration. Often seen in constrictive pericarditis.
- **Systolic and diastolic murmurs** are detailed in Table 2.1-2 and Figures 2.1-6, 2.1-7, and 2.1-8.

TABLE 2.1-2. **Differentiating Murmurs Based on Maneuvers**



MANEUVER	HEMODYNAMICS[a]	MITRAL VALVE PROLAPSE	HYPERTROPHIC CARDIOMYOPATHY	AORTIC STENOSIS	AR, MR, VSD
Squatting Valsalva: Release Leg raise	↑ venous return ↑ SVR ↑ venous return	↓ prolapse, delayed click, shorter murmur	↓ obstruction ↓ murmur	↑ ejection ↑ murmur	↑ murmur
Standing Valsalva: Strain	↓ venous return ↓ SVR	↑ prolapse, early click, longer murmur	↑ obstruction ↑ murmur	↓ ejection ↓ murmur	↓ murmur
Hand grip	↑ SVR	↓ prolapse, delayed click, shorter murmur	↓ murmur	↓ murmur	↑ murmur
Inspiration	↑ venous return (right heart) ↓ venous return (left heart)	↑ flow to right heart = ↑ right-sided murmurs ↓ flow to left heart = ↓ left-sided murmurs			

[a] Venous return: preload; systemic vascular resistance (SVR): afterload.

AR, Aortic regurgitation; *MR,* mitral regurgitation; *VSD,* ventricular septal defect.

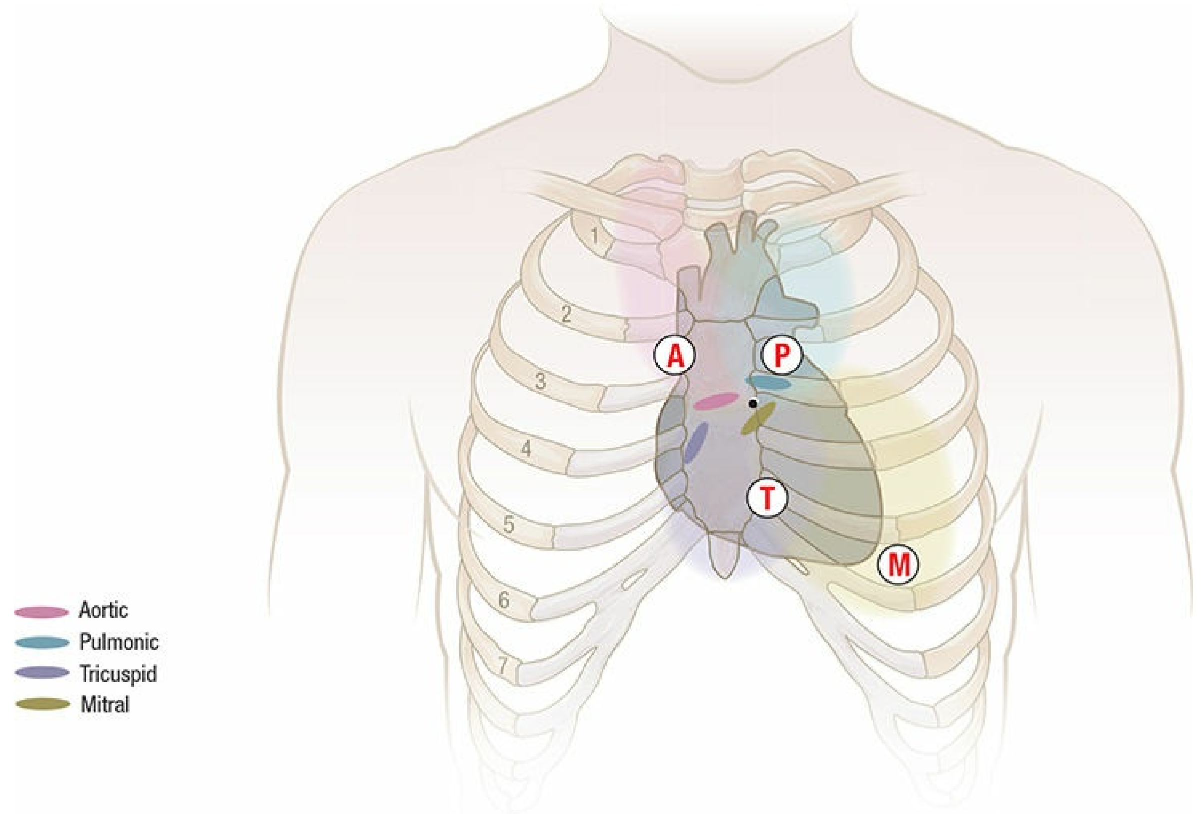
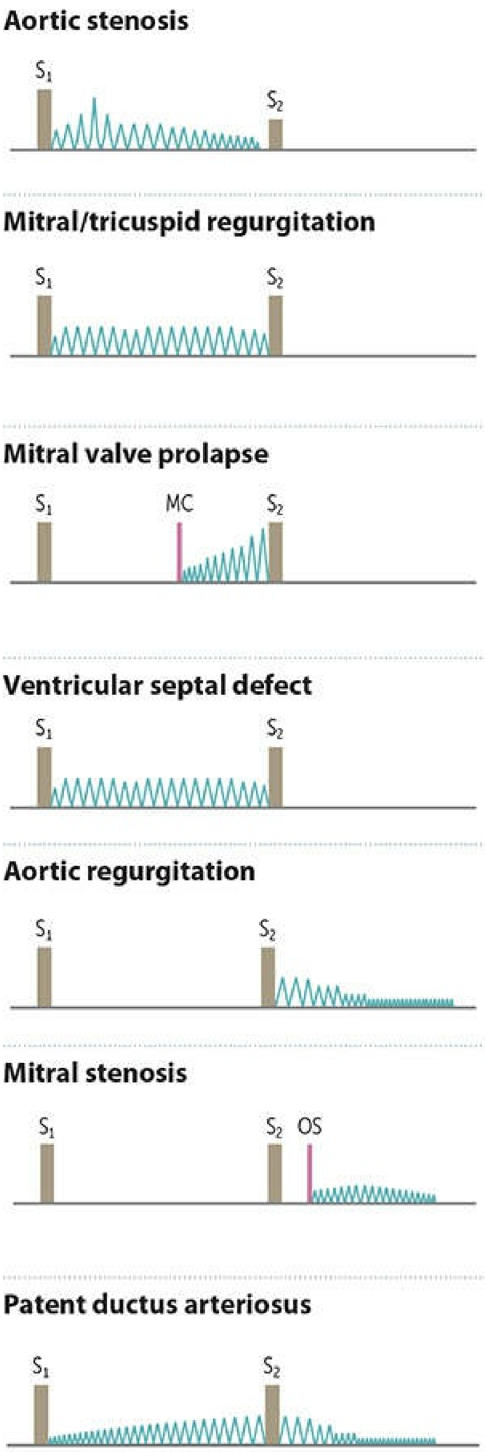


FIGURE 2.1-6. **Auscultation locations.** Auscultation sites are shown with associated valves. *A*, aortic valve; *M*, mitral valve; *P*, pulmonic valve; *T*, tricuspid valve. (Modified with permission from USMLE-Rx.com.)



Aortic stenosis

A harsh crescendo-decrescendo systolic ejection murmur heard best at the aortic valve area (parasternal 2nd right intercostal space [ICS]) or Erb's point (parasternal 3rd left ICS) that radiates to the carotids.

Mitral/tricuspid regurgitation

Mitral regurgitation: A holosystolic murmur heard best at the apex (midclavicular fifth left intercostal space [ICS]) that radiates to the axilla.

Tricuspid regurgitation: A holosystolic murmur heard best at the tricuspid valve (parasternal fourth left ICS).

Mitral valve prolapse

A midsystolic or late systolic crescendo murmur heard best at the apex (midclavicular fifth left ICS) with a preceding click (due to tensioning of cordae as mitral leaflets prolapse). Fig. 2.1-8 compares mitral valve prolapse and stenosis.

Ventricular septal defect

Holosystolic, harsh-sounding murmur heard best at tricuspid area (parasternal fourth left ICS). Larger ventricular septal defects (VSDs) have a lower intensity murmur than smaller VSDs.

Aortic regurgitation

A high-pitched "blowing" early diastolic decrescendo murmur heard best at the aortic valve (parasternal second right ICS).

Mitral stenosis

A mid to late low-pitched diastolic murmur preceded by an opening snap (mitral opening murmur) heard best at the apex (midclavicular fifth left ICS). The duration of the murmur correlates with the severity of mitral stenosis. Most often caused by rheumatic fever.

Patent ductus arteriosus

Continuous machine-like murmur that is loudest at S_2 and is best heard at the left infraclavicular area.

FIGURE 2.1-7. **Heart murmurs.** Visual representations of common heart murmurs are shown in relation to S_1 and S_2. *MC*, Midsystolic click; *OS*, opening snap. (Adapted with permission from USMLE-Rx.com.)

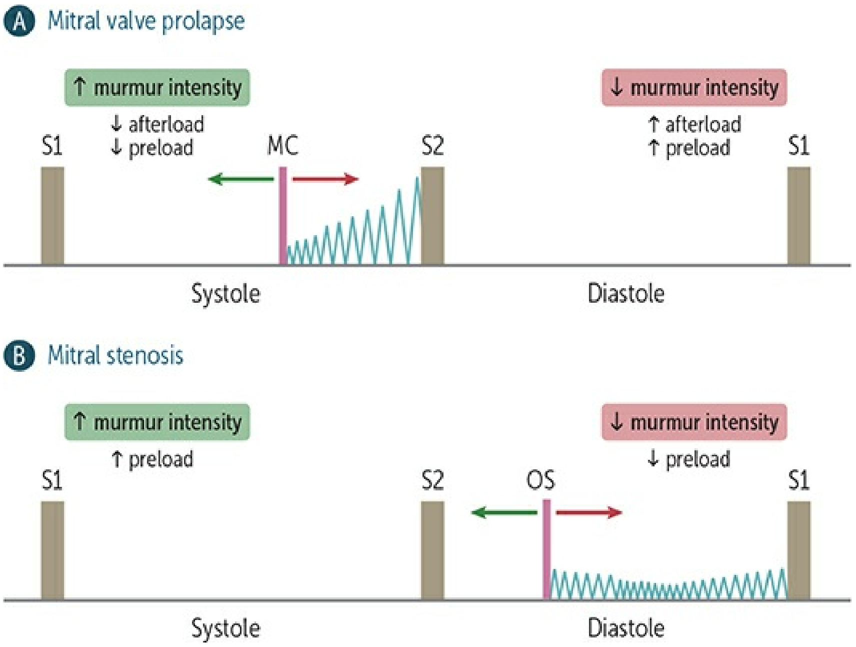

A Mitral valve prolapse
↑ murmur intensity
↓ afterload
↓ preload
↓ murmur intensity
↑ afterload
↑ preload
S1
MC
S2
S1
Systole
Diastole
B Mitral stenosis
↑ murmur intensity
↑ preload
↓ murmur intensity
↓ preload
S1
S2
OS
S1
Systole
Diastole

FIGURE 2.1-8. **Murmurs of mitral valve prolapse and mitral stenosis.** Visual representations of common heart murmurs are shown in relation to S_1 and S_2. *MC*, midsystolic click; *OS*, opening snap. (Adapted with permission from USMLE-Rx.com.)

- **Flow murmur:** Usually a soft murmur that is position dependent (very common and does not imply cardiac disease).

MNEMONIC

Systolic Murmurs

Change regurgitation (or insufficiency) to stenosis, and the stenosis to regurgitation in **"ARMS PITS"** to derive systolic murmurs.

Aortic stenosis
Mitral regurgitation (**M**itral valve prolapse)
Pulmonary stenosis
Tricuspid regurgitation

- **Gallops:**
  - **S_3 gallop:** A sign of fluid overload (eg, heart failure, mitral valve disease); often normal in younger patients and in high-output states (eg, pregnancy).
  - **S_4 gallop:** A sign of decreased compliance (eg, hypertension, aortic stenosis, diastolic dysfunction); usually pathologic but can be normal in younger patients and in athletes.

KEY FACT

More blood (↑ preload) = Increased murmur in everything except mitral valve prolapse (MVP) and hypertrophic obstructive cardiomyopathy (HOCM).

KEY FACT

Right-sided murmurs increase with inspiration. Left-sided murmurs increase with expiration.

- **Edema:**
  - **Pulmonary edema:** Left heart failure (fluid “backs up” into the lungs).
  - **Peripheral edema:** Right heart failure and biventricular failure (fluid “backs up” into the periphery), nephrotic syndrome, hepatic disease, lymphedema, hypoalbuminemia, and drugs.
- **Hands:**
  - **Finger clubbing:** Congenital cyanotic heart disease; endocarditis.
  - **Infective endocarditis:** Splinter hemorrhages, Osler nodes, Janeway lesions.
- **Peripheral pulses:**
  - **Increased:** Compensated aortic regurgitation (bounding pulses); coarctation (greater in arms than in legs); patent ductus arteriosus.
  - **Decreased:** Peripheral arterial disease; late-stage heart failure.
  - **Collapsing** ("waterhammer"): Aortic incompetence; AV malformations; patent ductus arteriosus; thyrotoxicosis, severe anemia.
  - **Pulsus paradoxus** (↓ systolic blood pressure [BP] >10 mm Hg with inspiration): Cardiac tamponade; pericardial constriction; also seen in obstructive lung diseases (eg, severe asthma), tension pneumothorax, and foreign body in airway.
  - **Pulsus alternans** (alternating weak and strong pulses): Cardiomyopathy; impaired left ventricular systolic function (LVF). Poor prognosis.
  - **Pulsus parvus et tardus** (weak and delayed pulse): Aortic stenosis.
  - **Jerky:** Hypertrophic obstructive cardiomyopathy (HOCM).
  - **Pulsus bisferiens** (bifid pulse/“twice beating”): Aortic regurgitation; combined aortic stenosis and aortic regurgitation, HOCM.

KEY FACT

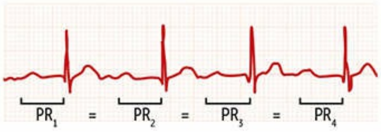
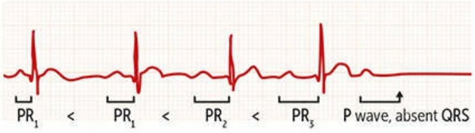
Atrial myxoma (benign tumor of the heart): Commonly in the left atrium on the interatrial septum. Patients may develop intermittent mitral obstruction, systemic embolization from tumor breakage, arrhythmias, or nonspecific symptoms (fever, weight loss). May present with atrial fibrillation or mimic infective endocarditis. On auscultation, tumor “plop” is audible. Tumor is visualized on echocardiography. Treatment: tumor resection.

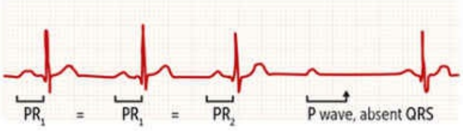
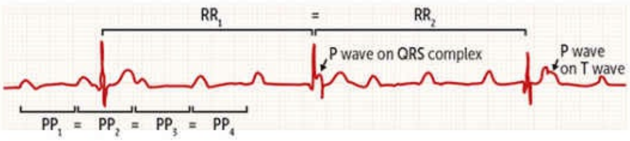
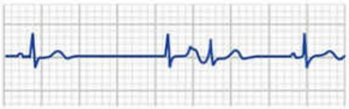
ARRHYTHMIAS

BRADYARRHYTHMIAS AND CONDUCTION ABNORMALITIES

Table 2.1-3 outlines the etiologies, clinical presentation, and treatment of common bradyarrhythmias and conduction abnormalities.

TABLE 2.1-3. **Bradyarrhythmias and Conduction Abnormalities**

TYPE/ETIOLOGY	SIGNS/SYMPTOMS	TREATMENT
Sinus bradycardia	**ECG findings:** Sinus rhythm. Ventricular rate <60 bpm	
Normal response to cardiovascular conditioning Can also result from sinus node dysfunction, AV nodal blocking drugs; therefore it is important to review medications	May be asymptomatic, but may also present with lightheadedness, syncope, chest pain, or hypotension	None if asymptomatic; if symptomatic: Initial Rx: ▪ First line: atropine ▪ Second line: transcutaneous pacing or dopamine/epinephrine infusion ▪ Third line: temporary transvenous pacing Definitive Rx: permanent pacemaker implantation
First-degree AV block 	**ECG findings:** PR interval >200 msec	
Can occur in normal individuals; associated with ↑ vagal tone, β-blocker, or CCB use	Asymptomatic	None necessary
Second-degree AV block (Mobitz type I/Wenckebach) 	**ECG findings:** Progressive PR lengthening until a dropped beat occurs (arrow); the PR interval then resets	
Drug effects (digoxin, β-blockers, CCBs) or ↑ vagal tone; right coronary ischemia or infarction Suggests progressively delayed AV node conduction; not always due to intrinsic disease	Usually asymptomatic	None if asymptomatic Stop the offending drug Atropine as clinically indicated

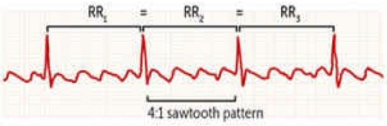
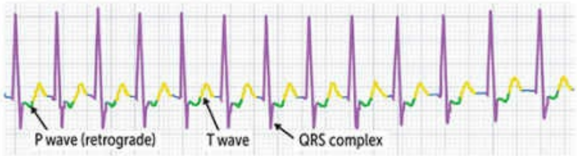
TYPE/ETIOLOGY	SIGNS/SYMPTOMS	TREATMENT
Second-degree AV block (Mobitz type II) 	**ECG findings:** Unexpected dropped beats without a change in PR interval	
Results from fibrotic disease of the conduction system or from acute, subacute, or prior MI Suggests intrinsic disease of His Purkinje system	Occasionally syncope; frequent progression to third-degree AV block	Pacemaker placement (even if asymptomatic)
Third-degree AV block (complete)  RR_1 = RR_2 P wave on QRS complex P wave on T wave PP_1 = PP_2 = PP_3 = PP_4	**ECG findings:** P and QRS waves occur regularly but at different rates (different PP and RR intervals shown in the figure; ie, atrial contraction is dissociated from ventricular contraction). Note: Some P waves are not visible or are partially visible due to fusion with QRS complex	
No electrical communication between the atria and ventricles Suggests disease of His Purkinje system	Syncope, dizziness, acute heart failure, hypotension, cannon A waves	Pacemaker placement
Sick sinus syndrome/tachycardia-bradycardia syndrome 	**ECG findings:** ECG shows an SA pause (no P waves generated, suggesting no activation at the SA node), followed by a junctional escape beat (QRS with no preceding P wave), and then reappearance of P waves (resumption of SA node activity). Other supraventricular tachyarrhythmias and bradyarrhythmias may occur intermittently in sick sinus syndrome (see ECGs earlier)	
Heterogeneous disorder that leads to intermittent supraventricular tachyarrhythmias and bradyarrhythmias	Secondary to tachycardia or bradycardia; AF and thromboembolism may occur → syncope, palpitations, dyspnea, chest pain, transient ischemic attack (TIA), and/or stroke	Most common indication for pacemaker placement Anticoagulate in AF/flutter to prevent systemic emboli

(Images adapted with permission from USMLE-Rx.com.)

TACHYARRHYTHMIAS

Tables 2.1-4 and 2.1-5 outline the etiologies, clinical presentation, and treatment of common supraventricular and ventricular tachyarrhythmias.

TABLE 2.1-4. **Supraventricular Tachyarrhythmias**

TYPE/ETIOLOGY	SIGNS/SYMPTOMS	TREATMENT
Sinus tachycardia	**ECG findings:** Sinus rhythm, ventricular rate >100 bpm	
Normal physiologic response to fear, pain, and exercise Can also be secondary to hyperthyroidism, volume contraction, infection, or pulmonary embolism (PE)	Palpitations, shortness of breath	Treat the underlying cause
Atrial flutter 	**ECG findings:** Regular rhythm; "sawtooth" appearance of P waves; atrial rate is usually 240–320 bpm, ventricular rate depends on conduction block through AV node (in example, atrial rate 300 bpm, ventricular rate 60 bpm)	
Circular movement of electrical activity around the atrium at a rate of approximately 300 times per minute. Reentrant circuit most commonly passes between inferior vena cava and tricuspid annulus (cavotricuspid isthmus). Interventions to ablate the cavotricuspid isthmus may break the reentrant circuit	Usually asymptomatic but can present with palpitations, syncope, and lightheadedness	Anticoagulation, rate control, and cardioversion guidelines as in atrial fibrillation (see earlier)
Atrioventricular nodal reentry tachycardia (AVNRT) 	**ECG findings:** HR about 150 bpm, with retrograde P waves. Note no P waves before the QRS complex	
A reentry circuit in the AV node depolarizes the atrium and ventricle nearly simultaneously	Palpitations, shortness of breath, angina, syncope, lightheadedness. AVRT and AVNRT are often indistinguishable on ECG. P waves may occur during or after QRS. These P waves may appear as a pseudo R′ in V_1, or pseudo S in inferior leads (II, III, aVF), a finding that supports AVNRT over AVRT	Cardiovert if hemodynamically unstable If stable, initial trial of vagal maneuvers (eg, Valsalva, carotid sinus massage, [CSM], ice immersion), followed by adenosine if ineffective CSM contraindicated in MI/TIA/stroke in previous 3 months, carotid stenosis/atheroma, ventricular fibrillation (VF)/ventricular tachycardia (VT), or previous adverse reaction to CSM
Atrioventricular reentrant tachycardia (AVRT)	**ECG findings:** Patient's baseline ECG may show preexcitation (see WPW syndrome later). During tachycardia, ECG is similar to AVNRT noted earlier. A retrograde P wave is often seen on the ST segment or T wave.	

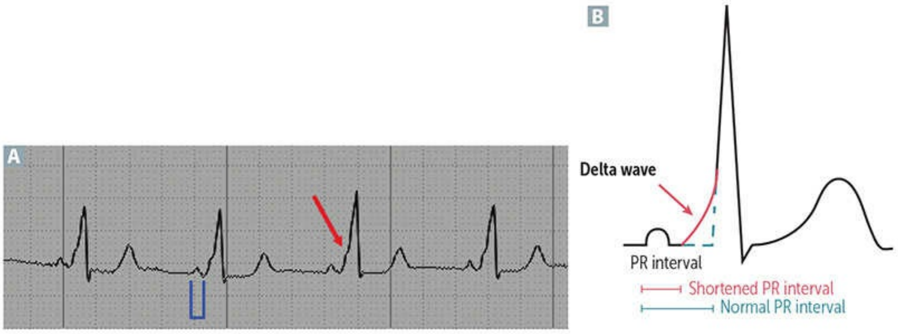
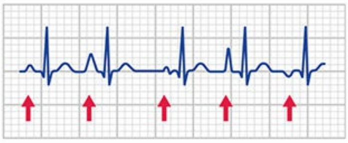
TYPE/ETIOLOGY	SIGNS/SYMPTOMS	TREATMENT
An ectopic connection between the atrium and ventricle that causes a reentry circuit AVRT is the most common arrhythmia associated with WPW syndrome (see later)	Palpitations, shortness of breath, angina, syncope, lightheadedness	Except for WPW, same as that for AVNRT
Wolff-Parkinson-White syndrome  A B Delta wave PR interval Shortened PR interval Normal PR interval		**ECG findings:** Early upslope of QRS complex (delta wave, *red arrow* in Image A) seen due to early activation of ventricles through accessory pathway. Thus, QRS is widened and PR interval is shortened *(blue)*. Compare with diagrammatic representation of ECG morphology in WPW (Image B).
WPW syndrome constitutes a group of ECG findings when there is an abnormal fast accessory conduction pathway from atria to ventricle (bundle of Kent) that bypasses the AV node and causes preexcitation of the ventricles. It is commonly associated with AVRT (see earlier).	Palpitations, dyspnea, dizziness, and rarely cardiac death	Observation for patients without symptoms Acute therapy is procainamide or amiodarone Supraventricular tachycardia (SVT) gets worse after AV nodal blockers (dangerous in WPW) Radiofrequency catheter ablation is curative
Atrial tachycardia	**ECG findings:** Rate >100 bpm; P wave with an unusual axis (inverted P in aVF suggests abnormal P axis) before each normal QRS	
Rapid ectopic pacemaker in the atrium (not sinus node)	Palpitations, shortness of breath, angina, syncope, lightheadedness	Adenosine can be used to unmask underlying atrial activity by slowing down the rate
Multifocal atrial tachycardia 	**ECG findings:** Three or more unique P-wave morphologies are visible *(red arrows)*; rate >100 bpm	
Multiple atrial pacemakers or reentrant pathways; associated with many cardiopulmonary conditions, eg, chronic obstructive pulmonary disease (COPD), hypoxemia, CHF	May be asymptomatic. At least three different P-wave morphologies	Treatment of underlying condition is first step Consider intravenous (IV) non-dihydropyridine CCBs and β-blockers for acute management If recurrent and symptomatic, oral non-dihydropyridine CCBs and β-blockers chronically (unless contraindicated)

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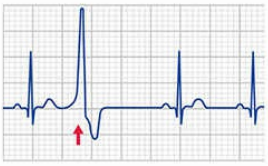
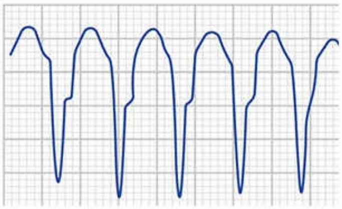
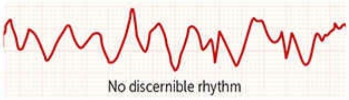
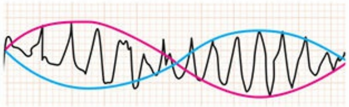
TABLE 2.1-5. Ventricular Tachyarrhythmias

TYPE/ETIOLOGY	SIGNS/SYMPTOMS	TREATMENT
Premature ventricular contraction (PVC) 	**ECG findings:** Early, wide QRS *(red arrow)* not preceded by a P wave; PVCs are usually followed by a compensatory pause	
Ectopic beats arise from ventricular foci. Associated with hypoxia, fibrosis, ↓ LV function, electrolyte abnormalities, and hyperthyroidism, but may be a normal finding	Usually asymptomatic, but may lead to palpitations	Treat the underlying cause. Decrease caffeine and alcohol consumption. If symptomatic, give β-blockers or, occasionally, other antiarrhythmics
Ventricular tachycardia (VT) 	**ECG findings:** Wide QRS complexes in a regular rapid rhythm; may see AV dissociation (P wave not seen in this example)	
Can be associated with coronary artery disease (CAD), MI, and structural heart disease	Three or more consecutive PVCs Nonsustained VT (lasts <30 seconds) is often asymptomatic; sustained VT (lasts >30 seconds) can lead to palpitations, hypotension, angina, and syncope Can progress to VF and death	Synchronized cardioversion if hemodynamically unstable Defibrillation if pulseless VT Antiarrhythmics (eg, amiodarone, lidocaine, procainamide) if stable
Ventricular fibrillation (VF) 	**ECG findings:** Totally erratic wide-complex tracing	
Associated with CAD and structural heart disease Also associated with cardiac arrest (together with asystole)	Syncope, absence of BP, no pulse	Immediate electrical defibrillation and advanced cardiac life support (ACLS) protocol
Torsades de pointes 	**ECG findings:** Polymorphous QRS with variations in amplitude and cycle length such that QRS appears to be twisting around an isoelectric base *(blue and red lines);* VT with rates between 150 and 250 bpm	
Associated with long QT syndrome, proarrhythmic response to medications, hypokalemia, hypocalcemia, hypomagnesemia, congenital deafness, and alcoholism	Can present with SCD; typically associated with palpitations, dizziness, and syncope	Synchronized cardioversion if hemodynamically unstable Defibrillation if pulseless Initial pharmacotherapy: magnesium Correct hypokalemia; withdraw offending drugs

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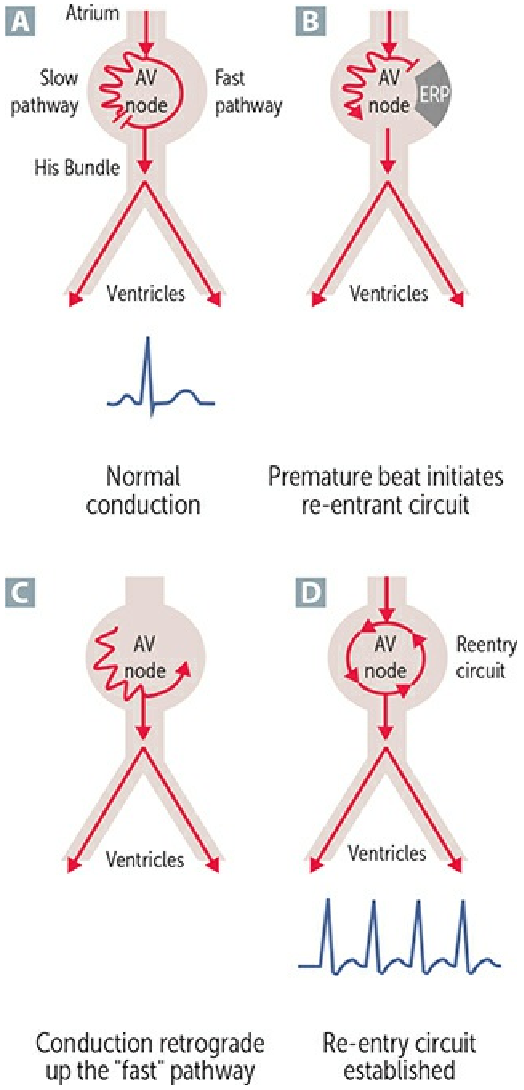
Mechanism of Tachyarrhythmias

The primary mechanisms of tachyarrhythmias include abnormal automaticity, triggered activity, and re-entry.

- **Abnormal automaticity:** Myocardial tissue that does not normally pace the heart (ie, no automaticity) may develop automaticity due to pathologic mechanisms (eg, ischemia, metabolic disturbances). Examples include accelerated idioventricular rhythm or multifocal atrial tachycardia.
- **Triggered activity:** Due to oscillations (called afterdepolarizations) in the membrane potential of cardiomyocytes that occur during or immediately after an action potential. If afterdepolarizations cross a critical threshold, a new action potential is generated. Examples include torsade de pointes.
- **Reentry:** Most common cause of tachyarrhythmias. Two distinct pathways connect to form a circuit. Conduction down this circuit could sustain a fixed and stable wavefront, which depolarizes the myocardium (Fig. 2.1-9). Examples include AVRT and AVNRT.



Normal conduction

Premature beat initiates re-entrant circuit

Conduction retrograde up the "fast" pathway

Re-entry circuit established

FIGURE 2.1-9. Mechanism of re-entry at the AV node. The AV node has a slow-conducting pathway with a short refractory period and a fast-conducting pathway with a long refractory period. During normal sinus rhythm, impulses are conducted down both pathways simultaneously but only transmitted to the His bundle down the fast pathway (myocardium is refractory once the slow impulse arrives) **(A)**. A premature atrial contraction could arrive when the fast pathway is still refractory but the slow pathway is able to conduct **(B)**. When the impulse from the slow pathway reaches the His bundle, the fast pathway is no longer refractory, thus allowing retrograde conduction up the fast pathway **(C)**. This impulse may continuously cycle through the fast and slow pathways, resulting in a reentry tachycardia, ie,

AVNRT **(D)**. Other reentrant tachycardias may share a similar mechanism. *ERP:* Effective refractory period. (Reproduced with permission from USMLE-RX.com.)

Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It results in disorganized atrial electrical activity and an irregularly irregular ventricular rhythm. This causes increased rates of stroke, heart failure, and mortality. See Table 2.1-4 for a summary.

Risk Factors

- AF is associated with increased age, hypertension, valvular disease, heart failure (HF), CAD, lung disease (PE, chronic lung disease, obstructive sleep apnea).
- Other reversible causes such as hyperthyroidism, electrolyte derangements, and substance use (caffeine or drugs) should be excluded on initial evaluation.

Pathophysiology

- Often triggered by irregularly depolarizing cells near the ostia of the pulmonary veins that result in disorganized atrial electrical activity.
- This results in an irregularly irregular pattern of ventricular contractions. Chronic AF may results in structural changes to the atrium.

Classification

- AF may be valvular (associated with mitral stenosis or prosthetic valve) or nonvalvular.
- It may be new-onset/recurrent, paroxysmal (self-limited), persistent (>7 days), long-standing (>12 months), or permanent (not looking to restore sinus rhythm).

History/PE

- Presentation ranges from asymptomatic to hemodynamically unstable. May have palpitations, fatigue, and dyspnea. Sometimes chest discomfort or even syncope.
- Importantly, can present with thromboembolic complications initially (eg, stroke, mesenteric).
- PE: Irregular pulse, irregular jugular venous pulsations.

Investigations

- **12-lead ECG:** Diagnosis confirmed on ECG (Fig. 2.1-10).

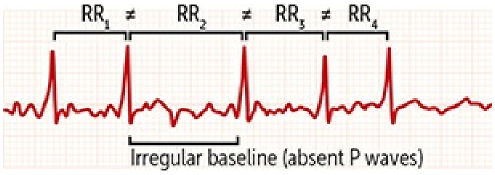

$RR_1 \neq RR_2 \neq RR_3 \neq RR_4$
Irregular baseline (absent P waves)

FIGURE 2.1-10. **ECG findings in atrial fibrillation.** No discernible P waves, with variable and irregular QRS response (RR interval varies irregularly). (Reproduced with permission from USMLE-Rx.com.)

- **Labs:** Electrolytes, complete blood count (CBC), and thyroid-stimulating hormone (TSH; hyperthyroidism should always be considered).
- **Transthoracic echocardiography (TTE):** To identify structural issues (eg, atrial size, valve disease).

Treatment

Patients with AF may require anticoagulation to prevent thromboembolism. Also, either a rate control or rhythm control strategy may be implemented to manage the arrythmia (see p. 32).

Q

A college-aged man passes out without any inciting factors and has no prodromal symptoms or signs of seizure. After recovery, his cardiac exam is unremarkable, and an ECG shows a slurred upstroke of the QRS. What are the next best steps?

- **Stroke prevention with long-term anticoagulation.**
  - Consider the risk of thromboembolism (estimated by CHADS-VASc score; refer to Key Fact) and risk of bleeding (HASBLED score) when deciding on anticoagulation. Generally, CHA2DS2-VASc score ≥2 in men and ≥3 in women merits anticoagulation with warfarin, dabigatran (thrombin inhibitor), or rivaroxaban (factor Xa inhibitor).
  - In patients with a low risk of bleeding, anticoagulation may be considered in men with a score ≥1 and women with a score ≥2.

KEY FACT

The **CHA$_2$DS$_2$-VASc** scoring system can estimate stroke risk in AF. Score of ≥2 in men or ≥3 in women: Recommend anticoagulation with a direct oral anticoagulant or warfarin. Anticoagulation may be considered at a lower score (1 in men, 2 in women):

- **C**HF (1 point)
- **H**TN (1 point)
- **A**ge ≥75 (2 points)
- **D**iabetes (1 point)
- **S**troke or TIA history (2 points)
- **V**ascular disease (1 point)
- **A**ge 65–74 (1 point)
- **S**ex **c**ategory (female) (1 point)

- **Stroke prevention with devices:**
  - Often, thrombi that cause stroke in AF form within the left atrial appendage (LAA), a small outpouching of the LA.
  - As an alternative to anticoagulation, minimally invasive occlusion of the LAA can prevent stroke. Considered for patients at risk for stroke but who cannot tolerate anticoagulation (eg, high bleeding risk).
  - Surgical closure of LAA is also possible in those who require cardiac surgery.
- **Rate control:**
  - Control of ventricular rate is equal to (and often preferred over) rhythm control with regard to mortality benefit. Target ventricular rate of <110 bpm is often used.
  - **Medications:** β-blockers (best initial Rx) and nondihydropyridine CCBs. Digitalis is sometimes used as an adjunct to improve rate control.
  - **Procedures:** Last resort for rate control is AV nodal ablation with implantation of a pacemaker.
- **Rhythm control:** Rhythm control does not improve mortality but may relieve symptoms and improve quality of life in select patients. Options include electrical cardioversion,

pharmacologic cardioversion, and catheter ablation.

- **Hemodynamically unstable patient:** Immediate electrical cardioversion is indicated.
- **Elective cardioversion and anticoagulation:** For stable patients requiring cardioversion.

A

This is WPW syndrome. The next best steps include prescribing procainamide, which treats arrhythmias, as well as referring for electrophysiologic evaluation and advising against physical activity. Syncope suggests unstable hemodynamics and raises suspicion for concurrent atrial fibrillation (AF). AV node blockers are contraindicated (adenosine, β-blockers, nondihydropyridine calcium channel blockers [CCBs]), even if AF develops.

  - **AF duration >48 hours:** High risk of thromboembolism. Three weeks anticoagulation given before cardioversion. Alternatively, transesophageal echocardiography can rule out LA thrombus, followed by cardioversion.
  - **AF duration <48 hours:** Lower thromboembolic risk. May cardiovert without prior anticoagulation. Some patients should still receive anticoagulation as soon as possible or after cardioversion based on thromboembolic risk.
  - Anticoagulation should be continued for 4 weeks post-cardioversion.
  - **Anticoagulant choice:** Nonvalvular AF: IV heparin, low-molecular-weight heparin (LMWH), warfarin, and new oral anticoagulants. Valvular AF: Only warfarin for mitral stenosis.
- **Pharmacologic cardioversion:** Drugs can be used to cardiovert and maintain sinus rhythm (eg, flecainide, propafenone, dofetilide, amiodarone, or IV ibutilide).
- **Ablation:**
  - A minimally invasive procedure that can electrically isolate pulmonary veins (from which abnormal cells that cause AF discharge) from the rest of the LA. This can result in restoration of sinus rhythm.
  - A similar procedure can be done surgically (Cox-maze procedure) for individuals requiring cardiac surgery.

KEY FACT

Evidence of Wolff-Parkinson-White syndrome (δ waves) on ECG calls for use of procainamide, not nodal blockers, for supraventricular tachycardias.

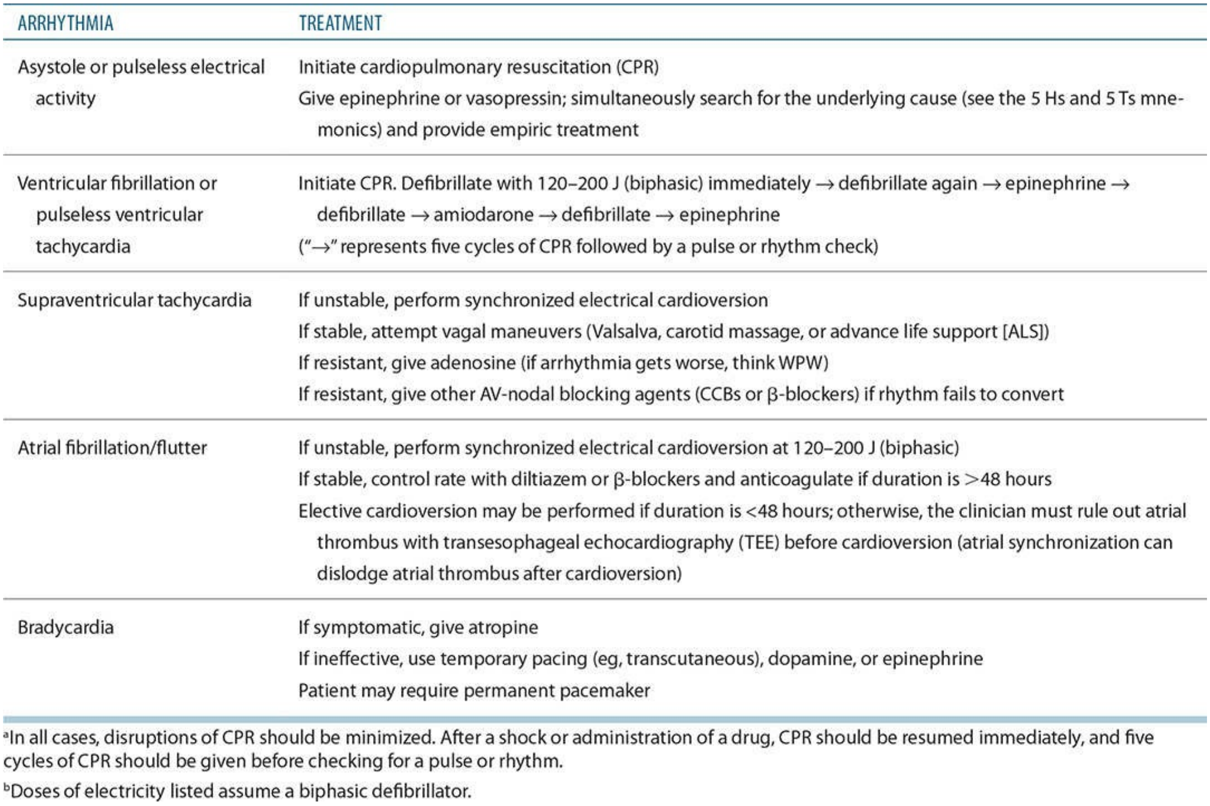
KEY FACT

Avoid vasopressors in hypovolemic shock until adequate fluid resuscitation has been provided. Vasopressors ↑ total peripheral resistance and BP but ↓ blood flow in tissues that undergo vasoconstriction. Autoregulation reduces the effect of vasopressors on vital organs so they maintain perfusion.

CARDIAC LIFE SUPPORT BASICS

Table 2.1-6 summarizes the basic management of cardiac arrhythmias in an acute setting. Table 2.1-7 compares cardioversion and defibrillation.

TABLE 2.1-6. **Management of Cardiac Arrhythmias**[a,b]

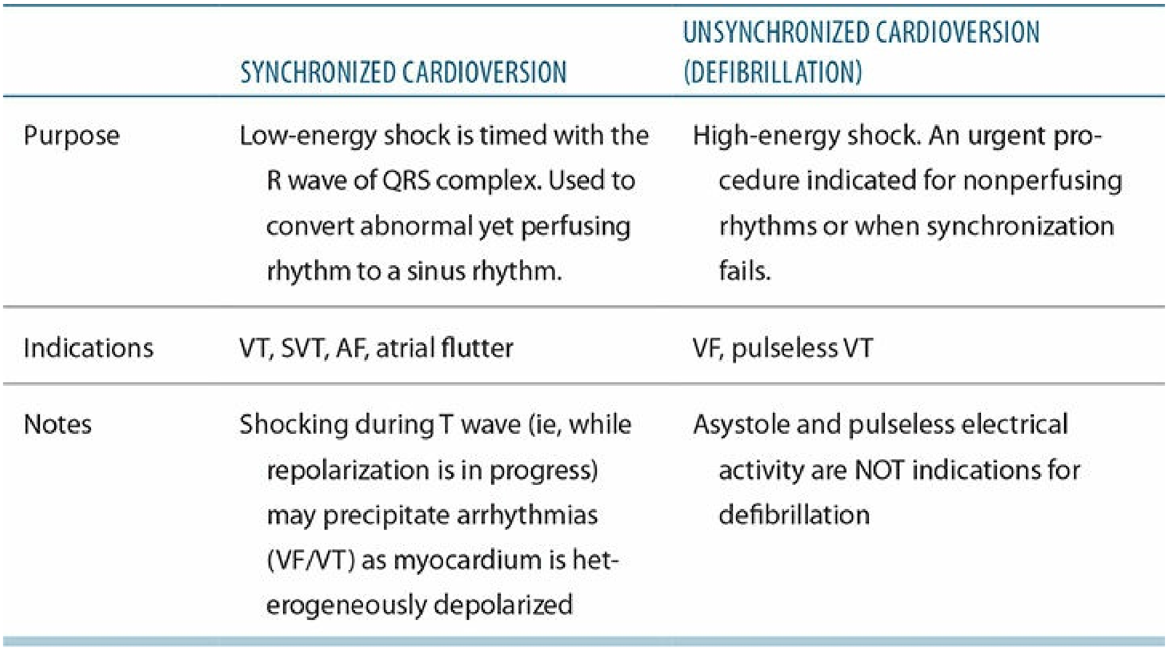


ARRHYTHMIA	TREATMENT
Asystole or pulseless electrical activity	Initiate cardiopulmonary resuscitation (CPR) Give epinephrine or vasopressin; simultaneously search for the underlying cause (see the 5 Hs and 5 Ts mnemonics) and provide empiric treatment
Ventricular fibrillation or pulseless ventricular tachycardia	Initiate CPR. Defibrillate with 120–200 J (biphasic) immediately → defibrillate again → epinephrine → defibrillate → amiodarone → defibrillate → epinephrine ("→" represents five cycles of CPR followed by a pulse or rhythm check)
Supraventricular tachycardia	If unstable, perform synchronized electrical cardioversion If stable, attempt vagal maneuvers (Valsalva, carotid massage, or advance life support [ALS]) If resistant, give adenosine (if arrhythmia gets worse, think WPW) If resistant, give other AV-nodal blocking agents (CCBs or β-blockers) if rhythm fails to convert
Atrial fibrillation/flutter	If unstable, perform synchronized electrical cardioversion at 120–200 J (biphasic) If stable, control rate with diltiazem or β-blockers and anticoagulate if duration is >48 hours Elective cardioversion may be performed if duration is <48 hours; otherwise, the clinician must rule out atrial thrombus with transesophageal echocardiography (TEE) before cardioversion (atrial synchronization can dislodge atrial thrombus after cardioversion)
Bradycardia	If symptomatic, give atropine If ineffective, use temporary pacing (eg, transcutaneous), dopamine, or epinephrine Patient may require permanent pacemaker

[a] In all cases, disruptions of CPR should be minimized. After a shock or administration of a drug, CPR should be resumed immediately, and five cycles of CPR should be given before checking for a pulse or rhythm.

[b] Doses of electricity listed assume a biphasic defibrillator.

TABLE 2.1-7. **Synchronized Cardioversion vs Defibrilation**



	SYNCHRONIZED CARDIOVERSION	UNSYNCHRONIZED CARDIOVERSION (DEFIBRILLATION)
Purpose	Low-energy shock is timed with the R wave of QRS complex. Used to convert abnormal yet perfusing rhythm to a sinus rhythm.	High-energy shock. An urgent procedure indicated for nonperfusing rhythms or when synchronization fails.
Indications	VT, SVT, AF, atrial flutter	VF, pulseless VT
Notes	Shocking during T wave (ie, while repolarization is in progress) may precipitate arrhythmias (VF/VT) as myocardium is heterogeneously depolarized	Asystole and pulseless electrical activity are NOT indications for defibrillation

KEY FACT

Treatments for unstable tachyarrhythmias:

Alive (has pulse) = Synchronized cardioversion (regardless of wide or narrow complex)
Dead (pulseless) = Defibrillate* (for VF, pulseless VT, or pulseless torsades)
*Pulseless electrical activity and asystole are not shockable rhythms. Rx = Epinephrine.

MNEMONIC

Possible causes of pulseless electrical activity—

5 Hs	5 Ts
Hypovolemia	**T**ablets: drug overdose, ingestion
Hypoxia	**T**amponade: cardiac
Hydrogen ion: acidosis	**T**ension pneumothorax
Hyper/**H**ypo: K+, other metabolite	**T**hrombosis: coronary
Hypothermia	**T**hrombosis: pulmonary embolism

CONGESTIVE HEART FAILURE

HF is a syndrome typified by a constellation of clinical symptoms (eg, breathlessness, ankle swelling) and signs (eg, JVP, pulmonary crackles). Structural or functional cardiac abnormalities result in elevated cardiac pressures and/or inadequate cardiac output at rest and/or on exertion. Etiologically, it can be related to valvular, pericardial, endocardial, vascular, or conduction abnormalities, among other causes. Risk factors include coronary heart disease, hypertension, cardiomyopathy, valvular heart disease, diabetes, and COPD (cor pulmonale).

CLASSIFICATION

Based on Ejection Fraction

HF is divided into distinct phenotypes based on left ventricular ejection fraction (LVEF).

- LVEF >40% is heart failure with reduced ejection fraction (HFrEF). Also known as systolic HF (Table 2.1-8).

TABLE 2.1-8. **Comparison of Systolic and Diastolic Dysfunction**

VARIABLE	SYSTOLIC DYSFUNCTION/HEART FAILURE WITH REDUCED EJECTION FRACTION (HFREF)	DIASTOLIC DYSFUNCTION/HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFPEF)
Patient age	Often <65 years of age	Often >65 years of age
Comorbidities	Dilated cardiomyopathy, valvular heart disease, MI	Restrictive or hypertrophic cardiomyopathy; renal disease or hypertension (HTN)
Physical exam	Displaced point of maximum impulse (PMI), S3 gallop ("KEN"-tuc-ky)	Sustained PMI, S4 gallop ("Tenn"-es-SEE)
X-ray of the chest (CXR)	Pulmonary congestion, cardiomegaly	Pulmonary congestion
ECG/echocardiography	Q waves, ↓ EF (<40%), dilation of the heart	Left ventricular hypertrophy (LVH), normal/preserved EF (>50%), abnormal LV diastolic indices

- LVEF 41% to 49% is heart failure with moderately reduced ejection fraction (HFmrEF).
- LVEF ≥50% is heart failure with preserved ejection fraction (HFpEF). For diagnosis of HFpEF there must be evidence of symptoms/signs of HF, structural/functional abnormalities supporting LV diastolic dysfunction, and/or increased natriuretic peptides. Also known as diastolic HF (see Table 2.1-8).
- There may also be primarily right ventricular (RV) heart failure (Table 2.1-9).

TABLE 2.1-9. **Left-Sided vs Right-Sided Heart Failure**

LEFT-SIDED CHF SYMPTOMS	RIGHT-SIDED CHF SYMPTOMS
Dyspnea predominates	Fluid retention predominates
Left-sided S3/S4 gallop	Right-sided S3/S4 gallop
Bilateral basilar rales	JVD
Pleural effusions	Hepatojugular reflux
Pulmonary edema	Peripheral edema
Orthopnea, paroxysmal nocturnal dyspnea	Hepatomegaly, ascites

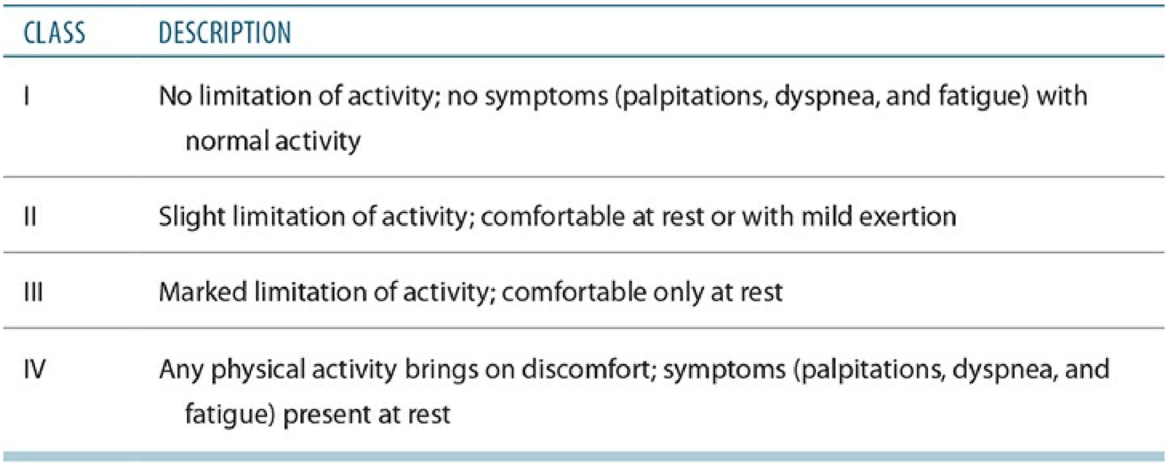
Based on Timing of Onset

Heart failure may be **chronic** (gradual progression with established diagnosis). Chronic HF may acutely worsen **(acute decompensated HF)**. Also, **acute** exacerbations of HF can occur without chronic HF.

Other Classifications

- **New York Heart Association (NYHA) classification** is based on functional status (Table 2.1-10).

TABLE 2.1-10. **NYHA Functional Classification of Congestive Heart Failure**



CLASS	DESCRIPTION
I	No limitation of activity; no symptoms (palpitations, dyspnea, and fatigue) with normal activity
II	Slight limitation of activity; comfortable at rest or with mild exertion
III	Marked limitation of activity; comfortable only at rest
IV	Any physical activity brings on discomfort; symptoms (palpitations, dyspnea, and fatigue) present at rest

- **Killip classification** grades HF severity after acute coronary syndrome (ACS). Predicts mortality at 30 days.

SYSTOLIC DYSFUNCTION/HEART FAILURE WITH REDUCED EJECTION FRACTION

↓ LVEF (<40%) and ↑ LV end-diastolic volumes result in typical HF symptoms and signs.

Etiology

- HFrEF (aka systolic HF) is caused by compensatory mechanisms (sympathetic nervous system [SNS] and renin-angiotensin-aldosterone system [RAAS] activation) to inciting conditions (eg, valvular disease, HTN) that may be acutely beneficial but may become maladaptive chronically (Fig. 2.1-11).

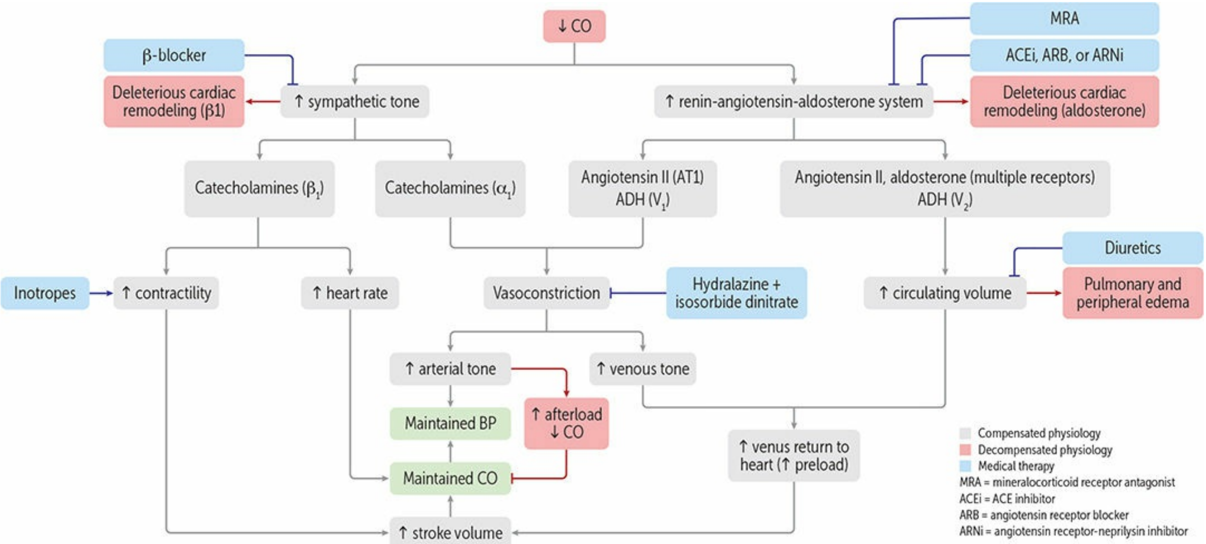

↓ CO
MRA
β-blocker
ACEi, ARB, or ARNi
Deleterious cardiac remodeling (β1)
↑ sympathetic tone
↑ renin-angiotensin-aldosterone system
Deleterious cardiac remodeling (aldosterone)
Catecholamines (β_1)
Catecholamines (α_1)
Angiotensin II (AT1) ADH (V_1)
Angiotensin II, aldosterone (multiple receptors) ADH (V_2)
Diuretics
Inotropes
↑ contractility
↑ heart rate
Vasoconstriction
Hydralazine + isosorbide dinitrate
↑ circulating volume
Pulmonary and peripheral edema
↑ arterial tone
↑ venous tone
Maintained BP
↑ afterload ↓ CO
↑ venus return to heart (↑ preload)
Maintained CO
↑ stroke volume
Compensated physiology
Decompensated physiology
Medical therapy
MRA = mineralocorticoid receptor antagonist
ACEi = ACE inhibitor
ARB = angiotensin receptor blocker
ARNi = angiotensin receptor-neprilysin inhibitor

FIGURE 2.1-11. **Pathophysiology of heart failure.** Activation of the RAAS and SNS may initially help the failing heart adapt by increasing contractility, heart rate, and circulating volume. However, deleterious cardiac remodeling may lead to worsening HF and pulmonary edema over time *(red boxes)*. Drugs that target the various maladaptive processes are shown *(blue boxes)*. (Reproduced with permission from USMLE-Rx.com.)

- Chronic activation of the SNS and RAAS results in cardiac and vascular remodeling (eg, hypertrophy, fibrosis, vasoconstriction), as well as sodium and water retention. Activation of the SNS leads to increased afterload (vasoconstriction/hypertension), whereas activation of the RAAS results in increased preload (salt and water retention).

KEY FACT

The most common cause of right-sided heart failure is left-sided heart failure.

History/PE

- Exertional dyspnea that progresses to orthopnea, paroxysmal nocturnal dyspnea (PND), and finally dyspnea at rest.
- Chronic cough, fatigue, and peripheral edema may be reported.
- Exam: Weight gain, bilateral pulmonary rales, increased JVP, positive hepatojugular reflex, peripheral edema, elevated and sustained LV impulse, and an S_3 gallop.

KEY FACT

Hyponatremia parallels the severity of HF and is an independent predictor of mortality in these patients.

Diagnosis

- HFrEF presents with the clinical syndrome of HF, with typical signs and symptoms, in addition to reduced EF(<40%).
- Studies that may support the diagnosis include the following:
  - **Best initial test:** Echocardiogram (transthoracic echocardiogram). ↓ EF helps establish HFrEF; structural abnormalities may help identify cause (eg, AF, old MI, or LVH).
  - **ECG:** May show MI, heart block, arrhythmia, or other diagnostic clues.
  - **CXR:** May show cardiomegaly, cephalization of pulmonary vessels, pleural effusions, vascular congestion, pulmonary edema, and prominent hila (Fig. 2.1-12).

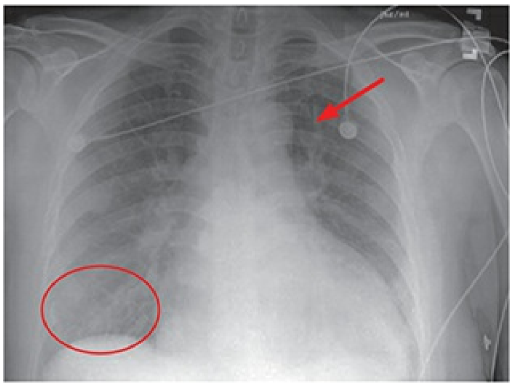


FIGURE 2.1-12. **X-ray of the chest (CXR) with evidence of congestive heart failure.** Frontal CXR demonstrates marked cardiomegaly, cephalization of vessels *(arrow)*, interstitial edema *(circle)*, and small left-sided pleural effusion, which raise concern for CHF. (Reproduced with permission from Tintinalli JE et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide.* 7th ed. New York, NY: McGraw-Hill; 2011.)

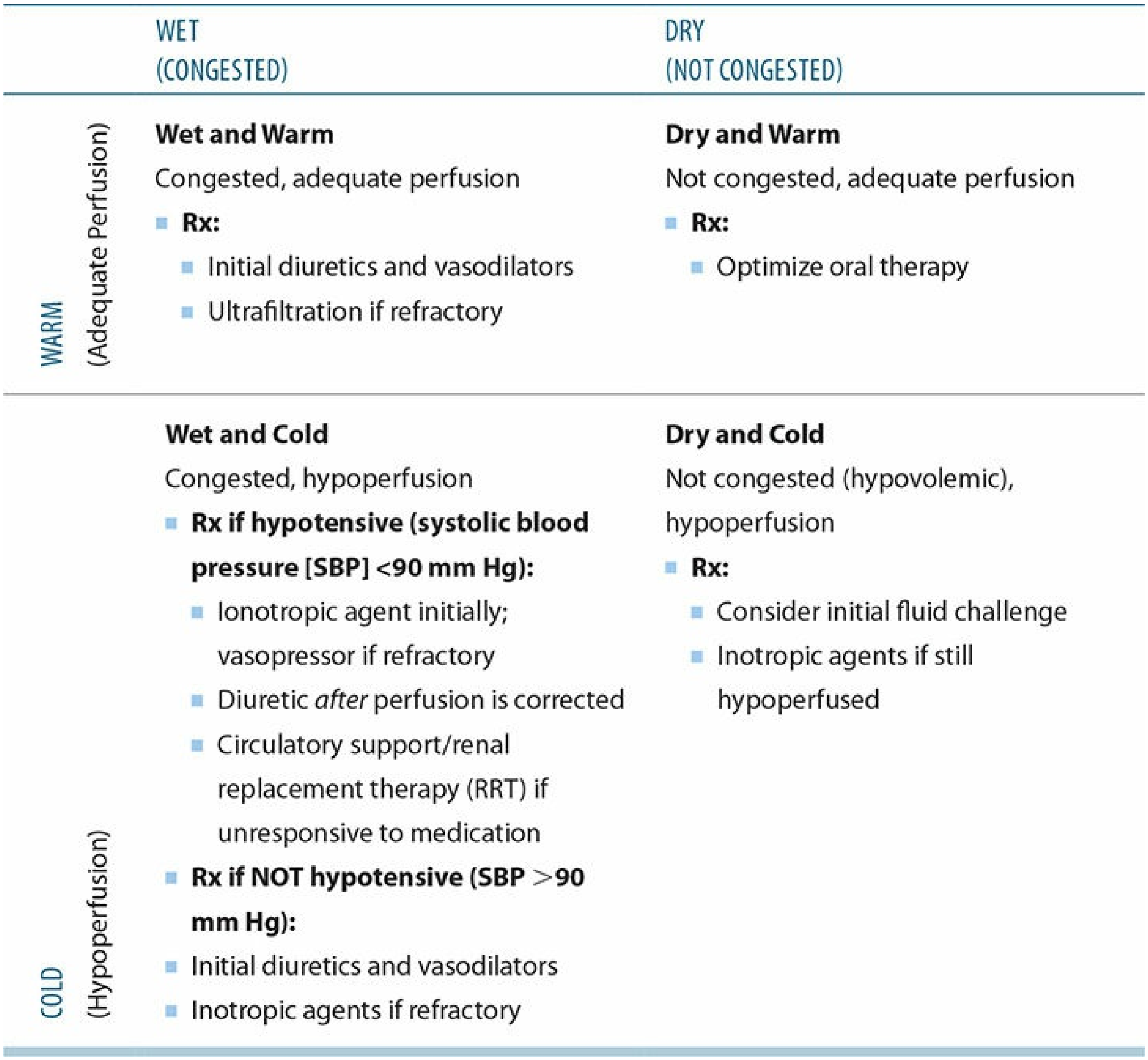
  - **Lab abnormalities:** Brain natriuretic peptide >500 pg/mL, ↓ CBC (anemia), ↑ creatinine (sometimes), ↓ sodium in later stages, ↑ or ↓ TSH/T_4 levels.

Treatment

Acute congestive heart failure:

- The first step in management is clinical identification of the hemodynamic profile. Specifically, the level of congestion (“wet” vs “dry”) and perfusion (“warm” vs “cold”) must be evaluated. Treatment is determined based on this evaluation, as illustrated in Table 2.1-11.

TABLE 2.1-11. **Hemodynamic Profiles in Heart Failure**



	WET (CONGESTED)	DRY (NOT CONGESTED)

WARM (Adequate Perfusion)	**Wet and Warm**
	Congested, adequate perfusion
	▪ **Rx:**
	  ▪ Initial diuretics and vasodilators
	  ▪ Ultrafiltration if refractory
		Dry and Warm
		Not congested, adequate perfusion
		▪ **Rx:**
		  ▪ Optimize oral therapy

COLD (Hypoperfusion)	**Wet and Cold**
	Congested, hypoperfusion
	▪ **Rx if hypotensive (systolic blood pressure [SBP] <90 mm Hg):**
	  ▪ Ionotropic agent initially; vasopressor if refractory
	  ▪ Diuretic *after* perfusion is corrected
	  ▪ Circulatory support/renal replacement therapy (RRT) if unresponsive to medication
	▪ **Rx if NOT hypotensive (SBP >90 mm Hg):**
	▪ Initial diuretics and vasodilators
	▪ Inotropic agents if refractory
		Dry and Cold
		Not congested (hypovolemic), hypoperfusion
		▪ **Rx:**
		  ▪ Consider initial fluid challenge
		  ▪ Inotropic agents if still hypoperfused

MNEMONIC

CXR findings in CHF diagnosis—ABCDE

Alveolar edema (“bat’s wings”)
Kerley **B** lines (interstitial edema)
Cardiomegaly
Dilated prominent upper lobe vessels
Effusion (pleural)

KEY FACT

Acute CHF management

- Upright positioning
- Vasodilators
- Diuretics
- Inotropes
- Oxygen if hypoxic
- Noninvasive positive-pressure ventilation
- Mechanical support

- In "warm and wet" patients (adequately perfused), loop diuretics and vasodilators are the best initial treatment.
- In "cold and wet" patients with hypotension (hypoperfused), loop diuretics may actually worsen perfusion by reducing intravascular volume. Therefore inotropic agents are used initially to augment perfusion, and direct vasodilators are added if BP can tolerate it.

Pharmacotherapy (Table 2.1-12):

TABLE 2.1-12. **Types of Diuretics**

CLASS	EXAMPLES	ADVERSE EFFECTS
Loop diuretics	Furosemide, ethacrynic acid, bumetanide, torsemide	Ototoxicity, hypokalemia, hypocalcemia, hyperuricemia, dehydration, gout
Thiazide diuretics	Hydrochlorothiazide, chlorothiazide, chlorthalidone	Hypokalemic metabolic alkalosis, hyponatremia, and hyper**GLUC** (hyper**G**lycemia, hyper**L**ipidemia, hyper**U**ricemia, hyper**C**alcemia)
Potassium -sparing agents	Spironolactone, eplerenone, triamterene, amiloride	Hyperkalemia, gynecomastia, sexual dysfunction; eplerenone does not have antiandrogenic effects that lead to gynecomastia
Carbonic anhydrase inhibitors	Acetazolamide	Hyperchloremic metabolic acidosis, neuropathy, NH3 toxicity, sulfa allergy
Osmotic agents	Mannitol	Pulmonary edema, dehydration; contraindicated in anuria and CHF

- **Oxygen** administered only if hypoxemic (SpO_2 <90%).
- **Loop diuretics** (most commonly) for preload reduction.
- **Vasodilators** to counter elevated filling pressures or LV afterload. Nitroglycerin is better for preload reduction (primarily venous vasodilation; useful in HF with predominant congestion) and nitroprusside for afterload reduction (arterial and venous vasodilation; useful in HF with severe HTN).
- **Inotropic agents** (milrinone, dobutamine, dopamine) and **vasopressors** (norepinephrine, high-dose dopamine, and vasopressin) may increase myocardial oxygen demand and worsen HF. Their use is indicated in hypotensive patients with impaired perfusion ("wet and cold"), who would not be able to tolerate diuretics. Once perfusion is restored, diuretics can be used.
- Other treatments include **sodium and fluid restriction** and **venous thromboembolism (VTE) prophylaxis** (LMWH, fondaparinux or unfractionated heparin).
- Initiation of β-**blockers is contraindicated** during decompensated HF, but should be restarted once the patient is euvolemic. If the patient was previously on β-blockers,

continuation may be considered, with or without dose reduction, based on the severity of decompensation.
- **Opiates (such as morphine) should be avoided** if possible.
- **Mechanical circulatory support** (MCS: intra-aortic balloon counterpulsation device, extracorporeal membrane oxygenation, short-term LV assist devices) considered in patients with HFrEF and severe hemodynamic compromise.
- **Correct underlying causes** such as arrhythmias, myocardial ischemia, and drugs (eg, CCBs, antiarrhythmics, nonsteroidal anti-inflammatory drugs [NSAIDs], alcohol, anemia, thyroid and valvular disease, high-output states).

Chronic heart failure:
- **Lifestyle:** Control comorbid conditions (eg, use of CPAP in sleep apnea may increase LVEF) and limit dietary sodium and fluid intake. Exercise as tolerated. Cardiac rehabilitation programs.
- **Pharmacologic therapy:**
  - **β-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitors (ACEIs/ARBs/ARNIs):** Help prevent remodeling of the heart and ↓ mortality and ↓ morbidity for NYHA class II–V patients. Avoid CCBs (can worsen edema).
  - **Ivabradine:** Reduces heart rate through SA nodal inhibition of the “funny channels.” Indicated in stable chronic HFrEF patients when pulse is >70 bpm despite receiving optimal HF therapy and maximum tolerable dose of β-blockers.
  - **Low-dose spironolactone:** Shown to ↓ mortality risk in patients with NYHA class II to V heart failure under specific conditions (LVEF <35% [<40% post-MI], estimated glomerular filtration rate [GFR] >30 mL/min, potassium <5.0 mEq/dL).
  - **Dapagliflozin or empagliflozin** are sodium-glucose transporter 2 (SGLT-2) inhibitors. Indicated for patients with HFrEF to ↓ hospitalization and mortality regardless of whether the patient has diabetes.
  - **Hydralazine and isosorbide dinitrate:** May ↓ mortality and ↓ morbidity in persistently symptomatic (NYHA III–V) Black Americans.
  - **Loop diuretics:** Shown to ↓ symptoms (no mortality benefit). Used in patients with NYHA II–V.
  - **Digoxin:** Increases cardiac contractility. Symptomatic control of dyspnea and ↓ frequency of hospitalizations.
  - **Acetylsalicylic acid (ASA) and a statin** are recommended if the underlying cause is a prior MI.

KEY FACT

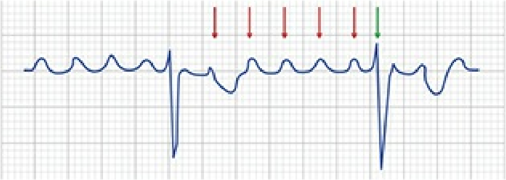
ACEIs/ARBs, ARNI, β-blockers, spironolactone or eplerenone, hydralazine-isosorbide dinitrate, and implantable defibrillators have mortality benefit in HFrEF (systolic dysfunction) but not HFpEF (diastolic dysfunction). Dapagliflozin and empagliflozin have mortality benefit in HFpEF and HFrEF. Loop diuretics and digoxin (as well as other positive inotropic agents) are for symptomatic relief only and confer no mortality benefit. CCBs may ↑ mortality.

KEY FACT

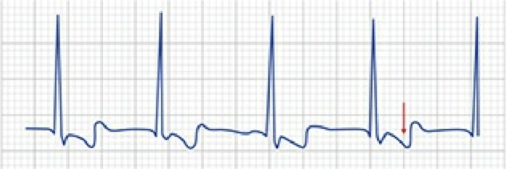
Loop diuretics lose calcium; thiazides take it in. Both cause hypokalemia and hyperuricemia.

- **Device therapy:**
  - ICD indicated in symptomatic patients (NYHA II/III) with an EF <35% at 40 days post-MI and 3 months post-revascularization. Shown to ↓ mortality.
  - ICD indicated in asymptomatic patients (NYHA I) with an EF <30% at 40 days post-MI and 3 months post-revascularization. Shown to ↓ mortality risk.
  - Cardiac resynchronization therapy (CRT, aka biventricular pacemaker) is most beneficial for symptomatic patients (NYHA class II/III/ambulatory IV symptoms) with LVEF ≤35%, sinus rhythm, LBBB with a QRS ≥150 msec, who are on optimal HF therapy.
  - Left ventricular assist device (LVAD), cardiac transplantation, other investigational therapies, or palliative care may be necessary in patients who are unresponsive to optimal medical and device therapies (such as ICD and CRT).

KEY FACT



Digoxin toxicity presents with cardiovascular, GI, and neurologic symptoms. Drugs such as amiodarone, β-blockers, verapamil, macrolides, or amphotericin B may precipitate digoxin toxicity. Cardiotoxicity may result in atrial tachycardia with AV block, as seen in the figure (P waves *[red arrows]* and only one QRS is conducted *[green arrow]*, ie, 5:1 block).



Digoxin effect refers to “normal” ECG changes in patients taking digoxin. Downsloping ST depression that looks like a “reverse tick” *(red arrow).*

(Images reproduced with permission from USMLE-Rx.com.)

HEART FAILURE WITH PRESERVED EJECTION FRACTION

HFpEF is defined by ↓ ventricular compliance with normal systolic function (LVEF ≥50%). The ventricle has either impaired active relaxation (secondary to **hypertension, ischemia, aging, and/or hypertrophy**) or impaired passive filling (**scarring from prior MI, restrictive cardiomyopathy**). Left ventricular end-diastolic pressure ↑, cardiac output remains essentially normal, and EF is normal or ↑.

History/PE

Associated with stable and unstable angina, shortness of breath, dyspnea on exertion, arrhythmias, MI, heart failure, and sudden death.

Diagnosis

- HFpEF presents with a clinical syndrome of HF with typical signs and symptoms in addition to preserved EF (≥50%). There must be evidence of structural and/or functional cardiac abnormalities supporting the presence of LV diastolic dysfunction.
- Investigations that may support the diagnosis include the following:
  - **Best initial test:** Echocardiogram (transthoracic echocardiogram). Establishes preserved EF (≥50%) and signs of diastolic dysfunction/raised LV filling pressures (LV mass index, LA volume index, E/e’ ratio at rest).
  - **Lab tests:** Natriuretic peptides generally elevated, although 20% of patients have normal values.
  - Invasive exercise testing.

Treatment

- **Best initial treatments:** Diuretics for symptom relief only (see Table 2.1-12).
- **Investigational therapy:** Empagliflozin is the only drug to reduce mortality in HFpEF.
- Screening for specific etiologies and instituting relevant treatments.
- Treatment of comorbidities (eg, maintain rate and BP control via β-blockers [first-line], ACEIs, ARBs, or CCBs).
- Digoxin and spironolactone are not beneficial in these patients.

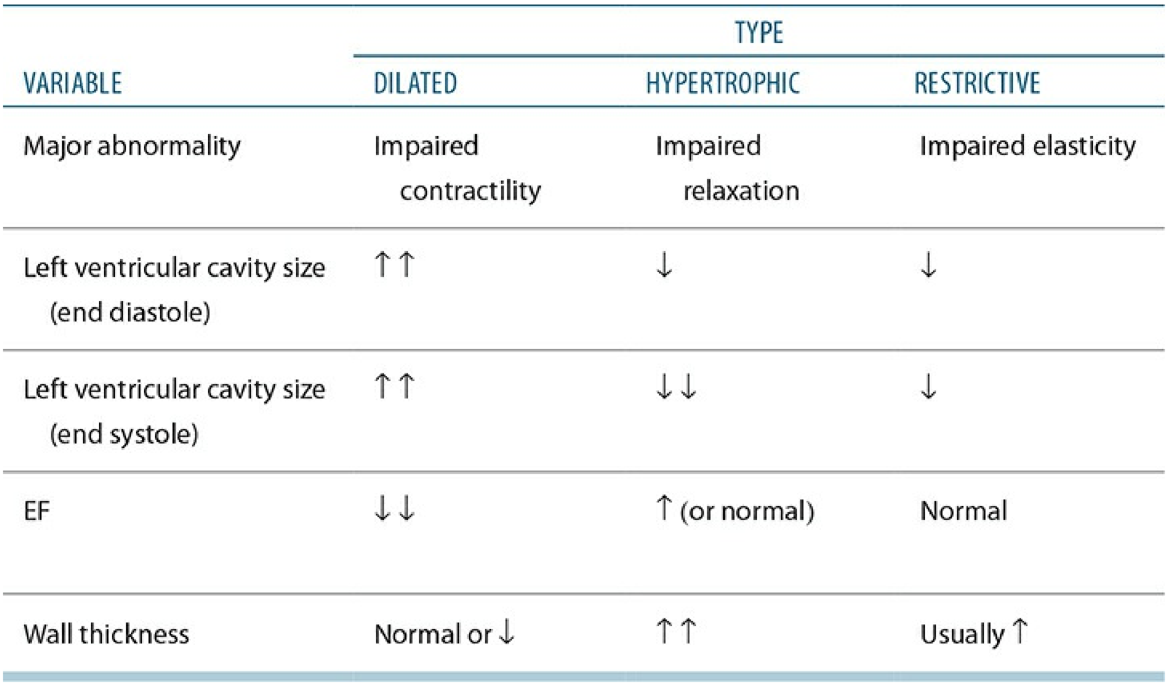
KEY FACT

Dapagliflozin and Empagliflozin reduce mortality in HFpEF.

CARDIOMYOPATHY

Myocardial disease; categorized as dilated, hypertrophic, or restrictive (Table 2.1-13 and Fig. 2.1-13). Pathology may be confined to the heart (primary) or due to systemic conditions affecting the heart (secondary).

TABLE 2.1-13. **Differential Diagnosis of Cardiomyopathies**



VARIABLE	TYPE		
	DILATED	HYPERTROPHIC	RESTRICTIVE
Major abnormality	Impaired contractility	Impaired relaxation	Impaired elasticity
Left ventricular cavity size (end diastole)	↑↑	↓	↓
Left ventricular cavity size (end systole)	↑↑	↓↓	↓
EF	↓↓	↑ (or normal)	Normal
Wall thickness	Normal or ↓	↑↑	Usually ↑

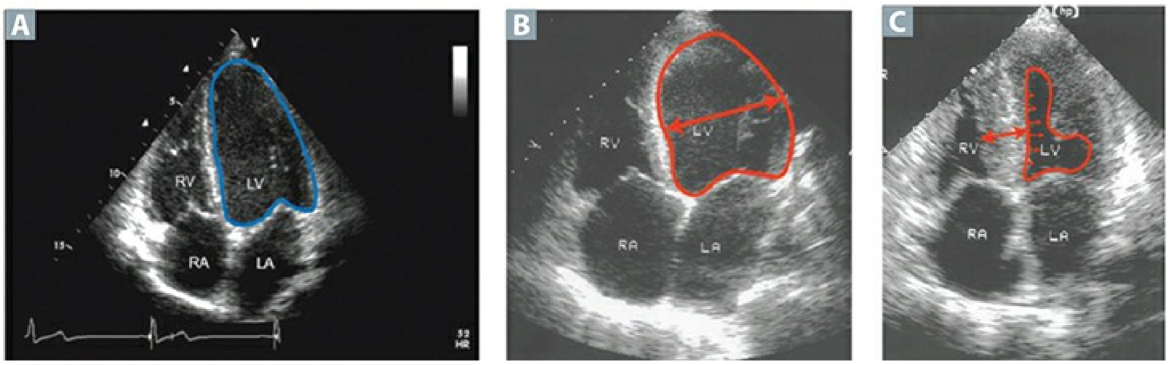


FIGURE 2.1-13. Cardiomyopathies. Echocardiogram four-chamber views of **(A)** a normal heart, **(B)** dilated cardiomyopathy, and **(C)** hypertrophic cardiomyopathy. (Reproduced with permission from Fuster V et al. *Hurst's The Heart.* 12th ed. New York, NY: McGraw-Hill; 2008.)

DILATED CARDIOMYOPATHY

LV dilation and ↓ EF must be present for diagnosis. Most cases are idiopathic or genetic, but secondary (and acquired) causes include alcohol, postviral myocarditis, postpartum status, drugs (doxorubicin, zidovudine, cocaine), radiation, endocrinopathies (thyrotoxicosis, acromegaly, pheochromocytoma), infection (coxsackievirus, HIV, Chagas disease, parasites), genetic factors, and nutritional disorders (wet beriberi). The most common cause of dilated cardiomyopathy (DCM) ***phenotype*** is myocardial ischemia; however, this is classified as a separate condition.

KEY FACT

An S_3 gallop signifies rapid ventricular filling in the setting of fluid overload and is associated with DCM. An S_3 gallop sounds similar to the word "KEN-tuc-ky."

History/PE

- Often presents with gradual development of CHF symptoms such as dyspnea on exertion and diffuse edema of the ankles, feet, legs, and abdomen.
- Exam often reveals displacement of the LV impulse, JVD, rales, an S_3/S_4 gallop, or mitral/tricuspid regurgitation.

KEY FACT

An S_4 gallop signifies a stiff, noncompliant ventricle and ↑ "atrial kick" and may be associated with hypertrophic cardiomyopathy. An S_4 gallop sounds similar to the word "Tenn-es-SEE."

Diagnosis

- **Best diagnostic test:** Echocardiography.
- CXR shows an enlarged, "balloon-like" heart and pulmonary congestion.

Treatment

- Address the underlying etiology (eg, alcohol use, endocrine disorders, infection).
- Treat CHF as noted in earlier section with lifestyle changes, and pharmacologic treatments.

Q

A man was admitted to the hospital for a CHF exacerbation with low EF. The patient is now ready for discharge, and his medications include furosemide and metoprolol. Assuming no contraindications, what medications would be appropriate to add to his treatment regimen?

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is a genetic condition with autosomal dominant inheritance characterized by impaired LV relaxation and filling (diastolic dysfunction) due to thickened ventricular walls. In HCM, asymmetric hypertrophy of the interventricular septum may occur, which may result in LV outflow tract obstruction and impaired ejection of blood, ie, HCM with obstruction (aka hypertrophic obstructive cardiomyopathy [HOCM]). HCM with obstruction is the most likely cause of SCD in young adults in the United States, mediated primarily by VF.

Note: Other causes of LVH include HTN (most common cause), aortic stenosis, and systemic diseases (glycogen/lysosomal storage diseases, Fabry, amyloid, sarcoid, and hemochromatosis), but these are considered separate entities from HCM.

KEY FACT

HOCM is the most common cause of sudden death in young, healthy athletes in the United States.

History/PE

- **Most common presentation:** Syncope or SCD in a young, healthy athlete.
- Patients are often asymptomatic but may also present with syncope, lightheadedness, dyspnea, palpitations, angina, or SCD.
- Key finding is a harsh systolic ejection crescendo-decrescendo murmur in the lower left sternal edge that ↑ with ↓ preload (eg, Valsalva maneuver, standing) and ↓ with ↑ preload (eg, passive leg raise).
- Symptoms worsen with exercise, diuretics, dehydration, ACEIs/ARBs, digoxin, and hydralazine.
- Exam also often reveals a sustained apical impulse, an S_4 gallop, paradoxical S_2, and an abnormal bifid or bisferiens pulse (sudden quick rise followed by a slower longer rise due to LV outflow tract obstruction).

Diagnosis

- **Best initial test:** Echocardiography is diagnostic and shows an asymmetrically hypertrophied interventricular septum. Dynamic obstruction of blood flow (due to systolic anterior motion of the mitral valve against hypertrophied septum) may also be seen (HOCM).
- ECG may be normal or show signs of LVH and nonspecific ST- and T-wave changes. Septal Q waves are common in HCM (inferior and lateral leads).
- CXR may reveal left atrial enlargement (LAE) secondary to mitral regurgitation.

KEY FACT

Athlete's heart may also present with LVH and must be differentiated from HCM. Characteristics of HCM that distinguish it from athlete's heart include positive family history, ECG features (presence of depolarization/repolarization abnormalities in HCM), and echocardiographic features (enlarged LA, ↓ LV cavity size, LV thickness >15 mm, focal septal hypertrophy, and LV diastolic dysfunction in HCM).

Treatment

- **Best initial treatment: β-blocker**s are the best initial therapy for symptomatic relief in both HCM and HOCM; nondihydropyridine CCBs (negative inotropic effect) and ventricular pacemakers are second-line agents.
- Digoxin and spironolactone are contraindicated, as they worsen obstruction in HOCM. Diuretics may help in HCM but are contraindicated in HOCM.
- Implantable defibrillators should be used in symptomatic HOCM patients.
- Patients should avoid intense athletic competition and training.
- Surgical options for HOCM with persistent symptoms include partial excision or alcohol ablation of the myocardial septum.
- Surgical septal myomectomy is reserved for patients when medical and catheter procedures fail.

KEY FACT

Infants born to mothers with diabetes are at risk of developing HCM caused by fetal hyperinsulinemia in response to maternal hyperglycemia. Most infants are asymptomatic, but some develop LV outflow tract obstruction and HF. Treatment is IV fluids and β-blockers. The condition spontaneously regresses by age 1.

A

Appropriate medications to add would be an ACEI (or ARB/ARNI), spironolactone, and empagliflozin (or dapagliflozin) to this patient’s current regimen. These have been shown to have a ⊕ mortality benefit in patients with HF with reduced EF.

ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA

Arrhythmogenic right ventricular dysplasia (ARVD) is a genetic disease with autosomal dominant inheritance. Myocytes are replaced with fibrofatty tissue, causing RV dilation, resulting in ventricular arrhythmias, HF, and SCD. It is the second most common cause of SCD in young people (after HOCM).

History/PE

- **Most common presentation:** Palpitations due to ventricular arrhythmias. Also may present with syncope, dyspnea, chest pain, SCD, or without symptoms.

Diagnosis

- Diagnosis is based on structural (echocardiography or MRI), histologic (endocardial biopsy), and ECG abnormalities, combined with family history.
- Echocardiography shows RV dilatation and wall motion abnormalities. ECG shows inverted T waves in V_1–V_3, with epsilon waves at the end of the QRS complex (Fig. 2.1-14).

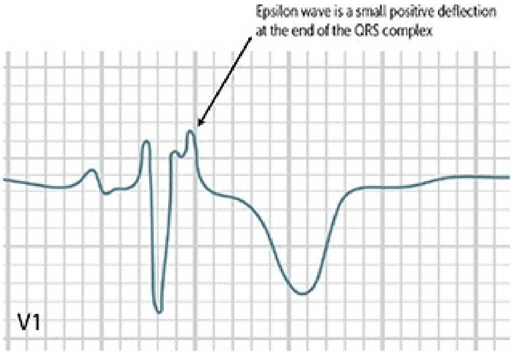

Epsilon wave is a small positive deflection at the end of the QRS complex
V1

FIGURE 2.1-14. **ECG in ARVD shows typical epsilon waves *(arrow)* in V_1.** (Reproduced with permission from USMLE-Rx.com.)

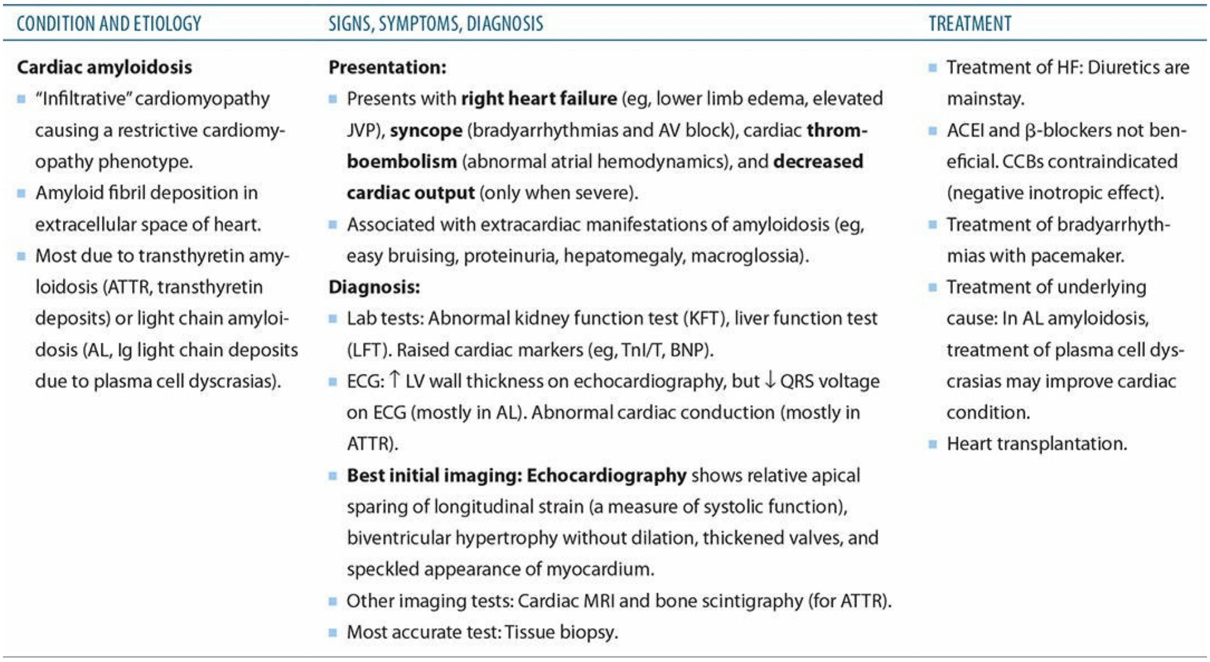
Treatment

- Avoid physical activity.
- Goals: Prevention of SCD (ICD), suppression of arrhythmia (β-blockers [first line], antiarrhythmic drugs [amiodarone, sotalol]), treatment of CHF (as described earlier), and anticoagulation (ie, for RV thrombus only).
- Invasive: ICD, heart transplantation (severe cases), genetic counseling for relatives.

RESTRICTIVE CARDIOMYOPATHY

Decreased elasticity of myocardium leading to impaired diastolic filling without significant systolic dysfunction (a normal or near-normal EF). It is caused by infiltrative disease (eg, amyloidosis, sarcoidosis, hemochromatosis [Table 2.1-14]), scleroderma, Loeffler eosinophilic endocarditis, endomyocardial fibrosis, or scarring and fibrosis (secondary to radiation).

TABLE 2.1-14. **Selected Secondary Cardiomyopathies**



CONDITION AND ETIOLOGY	SIGNS, SYMPTOMS, DIAGNOSIS	TREATMENT
Cardiac amyloidosis ▪ “Infiltrative” cardiomyopathy causing a restrictive cardiomyopathy phenotype. ▪ Amyloid fibril deposition in extracellular space of heart. ▪ Most due to transthyretin amyloidosis (ATTR, transthyretin deposits) or light chain amyloidosis (AL, Ig light chain deposits due to plasma cell dyscrasias).	**Presentation:** ▪ Presents with **right heart failure** (eg, lower limb edema, elevated JVP), **syncope** (bradyarrhythmias and AV block), cardiac **thromboembolism** (abnormal atrial hemodynamics), and **decreased cardiac output** (only when severe). ▪ Associated with extracardiac manifestations of amyloidosis (eg, easy bruising, proteinuria, hepatomegaly, macroglossia). **Diagnosis:** ▪ Lab tests: Abnormal kidney function test (KFT), liver function test (LFT). Raised cardiac markers (eg, TnI/T, BNP). ▪ ECG: ↑ LV wall thickness on echocardiography, but ↓ QRS voltage on ECG (mostly in AL). Abnormal cardiac conduction (mostly in ATTR). ▪ **Best initial imaging: Echocardiography** shows relative apical sparing of longitudinal strain (a measure of systolic function), biventricular hypertrophy without dilation, thickened valves, and speckled appearance of myocardium. ▪ Other imaging tests: Cardiac MRI and bone scintigraphy (for ATTR). ▪ Most accurate test: Tissue biopsy.	▪ Treatment of HF: Diuretics are mainstay. ▪ ACEI and β-blockers not beneficial. CCBs contraindicated (negative inotropic effect). ▪ Treatment of bradyarrhythmias with pacemaker. ▪ Treatment of underlying cause: In AL amyloidosis, treatment of plasma cell dyscrasias may improve cardiac condition. ▪ Heart transplantation.

CONDITION AND ETIOLOGY	SIGNS, SYMPTOMS, DIAGNOSIS	TREATMENT
Cardiac hemochromatosis ▪ Storage cardiomyopathy that is initially restrictive, later dilated. ▪ Intracellular iron accumulation systemically, including cardiomyocytes. ▪ Human homeostatic iron regulator protein mutations cause hereditary type (autosomal recessive [AR] with incomplete penetrance).	**Presentation:** ▪ Diastolic dysfunction and arrhythmias (followed by DCM at a later stage) in patients presenting with bronze skin, arthritis, diabetes, or cirrhosis. **Diagnosis:** ▪ Iron overload (↑ transferrin, ↑ ferritin, ↑ serum iron), liver dysfunction (↑ ALT, ↑ AST). ▪ Genetic testing, imaging (MRI, CXR), liver biopsy. ▪ Testing to establish cardiac involvement: Echocardiography (early diastolic dysfunction, late dilation, and systolic dysfunction). Cardiac MRI (best diagnostic test, can detect and quantify myocardial iron overload).	Standard treatment for HF (discussed earlier). Iron chelation therapy and therapeutic phlebotomy. Treatment of associated diseases (eg, diabetes).
Cardiac sarcoidosis ▪ Inflammatory cardiomyopathy that is initially restrictive and later dilated. ▪ Infiltration of myocardium by noncaseating granulomas. ▪ Unknown etiology.	**Presentation:** ▪ HF, arrhythmias (most common is **AV block**) or SCD associated with known extracardiac sarcoidosis (eg, cough, dyspnea, bilateral hilar lymphadenopathy, uveitis). **Diagnosis:** ▪ Initially, history, ECG, and echocardiography must have features suggestive of cardiomyopathy. ▪ Subsequent advanced imaging (fluorodeoxyglucose-positron emission tomography CT, cardiac MRI) supports diagnosis. ▪ Biopsy (either cardiac or extracardiac). ▪ Other possible causes must be excluded for diagnosis.	Standard HF treatment. Management of cardiovascular risks. Treatment of conduction abnormalities. Prevention of SCD if at risk (ICD implantation). Immunosuppressants. Periodic monitoring of cardiac function.
Endocrine Acromegaly, hyperthyroidism, hypothyroidism, DM, etc.	**Acromegalic cardiomyopathy:** Patient with enlarged hands, feet, and facial features and biventricular hypertrophy. Cardiac involvement shows diastolic and systolic dysfunction and valvular regurgitation. Leading cause of morbidity and mortality in patients with acromegaly.	Cardiac benefit in treating GH and IGH-1 levels early. Fifty percent of patients may recover LVEF. Optimize HF therapy.
	Diabetic cardiomyopathy: Diabetic patient with myocardial structural and functional abnormalities in absence of risk factors such as CAD, HTN, and valvular disease. Initially diastolic HF (LV hypertrophy, fibrosis), subsequently systolic HF (with LV dilation).	Optimize HF therapy. Optimize diabetes management.
Drugs Anthracyclines, cyclophosphamide, radiation.	**Chemotherapy-related cardiomyopathy:** Consider in a patient on cardiotoxic cancer treatments (eg, anthracyclines [most common], cyclophosphamide, trastuzumab) presenting with signs and symptoms of heart failure. **Diagnosis:** ▪ Any of the following: Reduced LVEF, symptoms/signs of HF, 5% ↓ in LVEF on serial monitoring with symptoms, or 10% ↓ without symptoms to <55% LVEF.	Optimization of cardiac risk factors. Baseline and serial cardiac monitoring (eg, echocardiograph, ECG). If HFrEF or significant ↓ in LVEF develops, hold medication and give optimal HF therapy. Consider secondary prevention for those at risk with ACEI/ARB, and β-blockers.

History/PE

Signs and symptoms of **right-sided heart failure** (JVD, peripheral edema, ascites, hepatomegaly) often predominate over left-sided failure, but dyspnea is the most common complaint.

Diagnosis

- Echocardiography is key for diagnosis, with rapid early filling and a near-normal or elevated EF. CXR, MRI, and cardiac catheterization are helpful for characterization (eg, sarcoid, amyloidosis).

- Cardiac biopsy may reveal fibrosis or evidence of infiltration.
- ECG frequently shows LBBB; low voltages are seen in amyloidosis.

Treatment

Treat the underlying cause. Therapeutic options are limited and are generally palliative only. Medical treatment includes cautious use of diuretics for fluid overload and vasodilators to ↓ filling pressure.

Q

A woman with HTN and prior MI has an exam notable for a displaced PMI, an S_3, a nonelevated JVP, and bibasilar rales. What is the next best step in diagnosis?

SECONDARY CARDIOMYOPATHY

- Secondary cardiomyopathies are caused by systemic diseases that affect the heart.
- Classified into infiltrative (hemochromatosis), inflammatory (sarcoidosis), endocrine (acromegaly, hyperthyroidism/hypothyroidism, diabetes mellitus [DM]), and drug induced (anthracyclines, cyclophosphamide, radiation). Some examples are provided in Table 2.1-14.

KEY FACT

Fifty to seventy percent of patients with AL amyloidosis have cardiac involvement, and this is the main prognostic determinant.

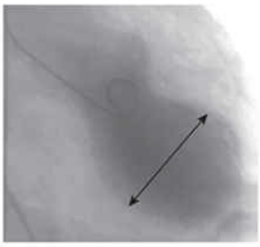
A

This patient has evidence of DCM. An echocardiogram would be the next best diagnostic step.

OTHER CARDIOMYOPATHIES

Table 2.1-15 describes myocarditis, peripartum cardiomyopathy, and Takotsubo cardiomyopathy.

TABLE 2.1-15. **Other Cardiomyopathies: Myocarditis, Peripartum Cardiomyopathy, and Takotsubo Cardiomyopathy**

CONDITION	ETIOLOGY	SIGNS, SYMPTOMS, DIAGNOSIS	TREATMENT
Myocarditis	Acute or chronic myocardial inflammation resulting in myocyte necrosis and fibrosis. Variable etiology, eg, infections (viral, bacterial, rickettsial, fungal), autoimmune.	**Presentation:** ▪ Healthy individual with acute decompensated HF and arrhythmia. ▪ May have fever, chills, chest pain, palpitations, syncope, or SCD. May have history of recent flulike illness. **Diagnosis:** ▪ Most often clinical. Supported by inflammatory markers, ECG, and echocardiography. ▪ **Most accurate test:** Myocardial biopsy (rarely done).	Treat CHF and arrhythmia (as earlier). Temporary transvenous pacing for complete heart block. Cardiac transplantation, LVAD, ECMO in severe cases, if indicated.
Peripartum	Unknown and likely multifactorial; some research suggests a predisposition in those with DCM-associated mutations.	**Presentation:** Peripartum woman with dyspnea, orthopnea, paroxysmal nocturnal dyspnea, pedal edema, and hemoptysis. **Diagnosis:** ▪ HF at end of pregnancy (usually ≥ 36 weeks) or in the 5 months after delivery. ▪ Echocardiography: LV dysfunction (LVEF <45%); the LV may or may not be dilated. ▪ No identifiable cause.	Treated as CHF (see earlier). Avoid teratogens (ACEIs, ARBs, ARB/neprilysin-inhibitors, and aldosterone receptor antagonists). Use diuretics, β-blockers, or hydralazine + nitrate if intrapartum. Echocardiogram monitoring biannually. Avoid future pregnancy if persistent EF <50%, especially if persistent EF <25%.
Takotsubo cardiomyopathy 	"Broken heart syndrome." Caused by severe psychological stress, without CAD.	**Presentation:** Older woman with symptoms of ACS, recent psychological stress, and no CAD. **Diagnosis:** ▪ LV apical ballooning on angiography with nonobstructive coronary angiography. ▪ Cardiac enzymes may be elevated, ECG may show ST elevation.	Initially managed as ACS. Subsequent treatment as HFrEF. Serial echocardiography.

(Image adapted with permission from Gangadhar TC et al. Takotsubo cardiomyopathy in a patient with esophageal cancer: A case report. *J Med Case Rep*. 2008;2:379. Published 2008 Dec 8. doi:10.1186/1752-1947-2-379.)

CORONARY ARTERY DISEASE

Also known as ischemic heart disease (IHD) or atherosclerotic heart disease. Clinical manifestations include stable and unstable angina, shortness of breath, dyspnea on exertion, arrhythmias, MI, HF, and sudden death.

Risk factors include the following:

- DM
- Family history of premature CAD (men <55 years of age, women <65 years of age).
- Smoking
- Hyperlipidemia

- Abdominal obesity
- HTN
- Age (men >45 years of age, women age >55 years of age)
- Male sex
- CAD risk equivalents include DM, symptomatic carotid artery disease, peripheral arterial disease, chronic kidney disease, and abdominal aortic aneurysm (AAA).

KEY FACT

Major risk factors for CAD include advanced age, male sex, ↑ LDL cholesterol, ↓ HDL cholesterol, HTN, a family history, and smoking. MI in menstruating women is rare.

ANGINA PECTORIS

Substernal chest pain secondary to myocardial ischemia (O_2 supply and demand mismatch). This is most often caused by atheroma (likely >70% stenosis of a coronary vessel). Less frequently caused by anemia, aortic stenosis, tachyarrhythmias, HCM, and small vessel disease.

History/PE

- The classic triad consists of (1) substernal chest pain that is (2) provoked by stress or exertion and is (3) relieved by rest or nitrates (stable angina).
- If the chest pain meets 3/3 of these characteristics, it is considered **typical chest pain**. If the chest pain meets 2/3 of these characteristics, it is considered **atypical chest pain**.
- The duration of stable angina is usually from 2 to 10 minutes (ACS is normally 10–30 minutes in duration).
- Pain can radiate to the neck or arm and may be associated with shortness of breath, nausea/vomiting, diaphoresis, dizziness, or lightheadedness.
- Pain is usually described as dull, squeezing, tightness, or pressure-like (Patients often describe it as “someone sitting on my chest”).
- Ischemic pain is not tender, positional, or pleuritic.

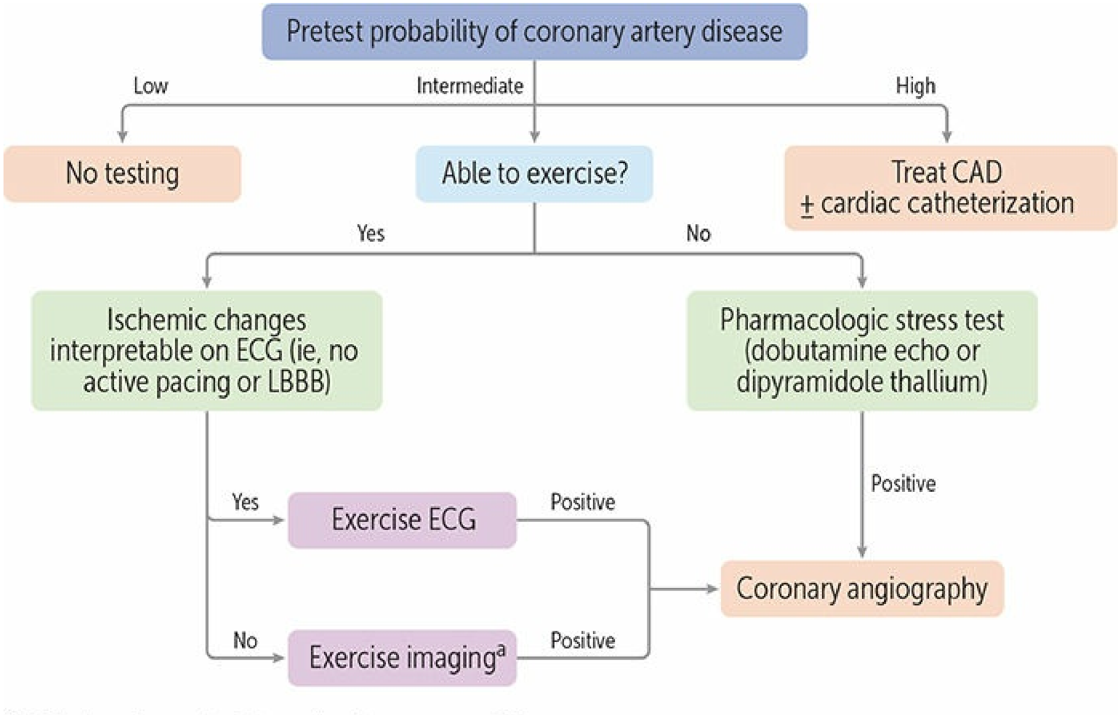
KEY FACT

Chest pain that is sharp/stabbing (pleuritic chest pain) or chest pain that changes with position, breathing, or touch is less likely to be ischemic.

Diagnosis

- **Best initial test:** ECG for any type of chest pain. It is usually normal in angina pectoris, but it may show ST depression, flat or inverted T waves, or signs of past MI.
- **Cardiac enzymes (CK-MB/troponin):** Stable angina will have normal troponins. These are usually drawn in the emergent setting subsequently after the ECG.
- **CXR:** This is to primarily help rule out other causes of chest pain, like aortic dissection (widened mediastinum), esophageal perforation (widened mediastinum/pleural effusion), PE, or pneumonia (pleural effusion/lung consolidation).
- **Stress testing:** Exercise or pharmacologic stress tests detect inducible myocardial

ischemia. Figure 2.1-15 details diagnostic test selection in patients with suspected stable angina.


Pretest probability of coronary artery disease
Low
Intermediate
High
No testing
Able to exercise?
Treat CAD
± cardiac catheterization
Yes
No
Ischemic changes interpretable on ECG (ie, no active pacing or LBBB)
Pharmacologic stress test (dobutamine echo or dipyramidole thallium)
Positive
Yes
Exercise ECG
Positive
Coronary angiography
No
Exercise imaging^a
Positive

[a] If LBBB, then pharmacological stress imaging or coronary CTA.

FIGURE 2.1-15. **Selections of appropriate investigation for patients with suspected stable angina.** Examples where ECG cannot be interpreted regarding ischemic changes include LBBB or paced ventricular rhythm. (Reproduced with permission from USMLE-Rx.com.)

- Stress tests are appropriate for diagnosis of CAD among patients with intermediate pretest probability (predictive value is low with low pretest probability).
- β-blockers, CCBs, and nitrates are held 48 hours prior to stress test (cause false-negative results).
- ST-segment or wall-motion changes (using echo) with exercise or pharmacologic stress (dobutamine echo or dipyridamole thallium) are diagnostic of CAD.

KEY FACT

Dipyridamole and adenosine stress test are **contraindicated** in:

1. Active bronchospasm/reactive airway disease (ie, asthma)
2. Second-degree or third-degree heart block, sick sinus syndrome, or severe bradycardia
3. SBP <90 mm Hg
4. With methylxanthines

- **Coronary angiography or CT coronary angiogram:** Coronary angiography, or a less invasive diagnostic test, CT coronary angiogram (availability varies among centers), may be used as a last resort if ECG or stress testing is equivocal.
- Rule out pulmonary, GI, or other cardiac causes of chest pain.

KEY FACT

Coronary Steal Syndrome

Adenosine and dipyridamole are coronary vasodilators that dilate normal coronary arteries more than rigid stenosed arteries. These drugs may cause perfusion to improve in normal vessels and decrease in diseased vessels ("steal of flow") which can result in detectable ischemia. Vasodilator stress tests do not rely on inducing coronary steal, although sometimes they cause it.

Differential Diagnosis

- **Gastroesophageal reflux disease (GERD):** History of hoarseness, bad taste, and cough; relief of symptoms with proton pump inhibitors confirms diagnosis.
- **Musculoskeletal/costochondritis:** Tenderness to palpation and movement.
- **Pneumonia/pleuritis:** Pain worsening with breathing (pleuritic) and often accompanied by fever and productive cough.
- **Pulmonary embolism:** Shortness of breath/hypoxia, tachycardia, hemoptysis, signs of deep vein thrombosis on physical exam, history of cancer, or recent surgery. Chest pain may also be pleuritic.
- **Aortic dissection:** Tearing chest pain that radiates to the back along with unequal radial pulses.
- **Esophageal perforation:** History of vomiting/recent endoscopy with presentation of fever, chest pain, crepitus/subcutaneous emphysema on physical exam.
- **Anxiety:** Patients may have history of panic disorder or anxiety attacks.
- **Shingles:** Pain and vesicular rash in a unilateral bandlike (dermatomal) distribution that does not cross the midline.

Treatment

- **Chronic stable angina:** ASA and antianginal drugs (see later).
  - β-blockers are the first-line therapy for chronic stable angina. They work by reducing myocardial contractility and heart rate (reduced oxygen demand relieves ischemia). Nondihydropyridine CCBs (verapamil, diltiazem) are an alternative that work through a similar mechanism.
  - Nitrates (eg, nitroglycerin) relieve pain by dilating capacitance veins (↓ preload) resulting in ↓ in LV end-diastolic pressure and wall stress.
  - Ranolazine is used in refractory angina and reduces intracellular calcium in myocytes, thus allowing complete relaxation during diastole, ↓ myocardial wall stress and end-diastolic pressure.
- Antiplatelet drugs as indicated (eg, aspirin, clopidogrel). Initiate risk factor reduction (eg, smoking, cholesterol, HTN) and start ACEIs/ARBs, lipid-lowering therapies (ie, statins), and smoking cessation. Hormone replacement therapy is not protective in postmenopausal women.

PRINZMETAL (VARIANT) ANGINA

- Mimics angina pectoris but is caused by vasospasm of smooth muscles of the coronary arteries.
- Typically occurs in young smokers (age <50 years) with minimal risk factors for atherosclerosis.
- **Treatment:** Non-dihydropyridine CCBs with or without long-acting nitrates. **Aspirin is**

avoided, as it can aggravate the ischemic attacks. β**-blockers are contraindicated,** as they can ↑ vasospasm.

KEY FACT

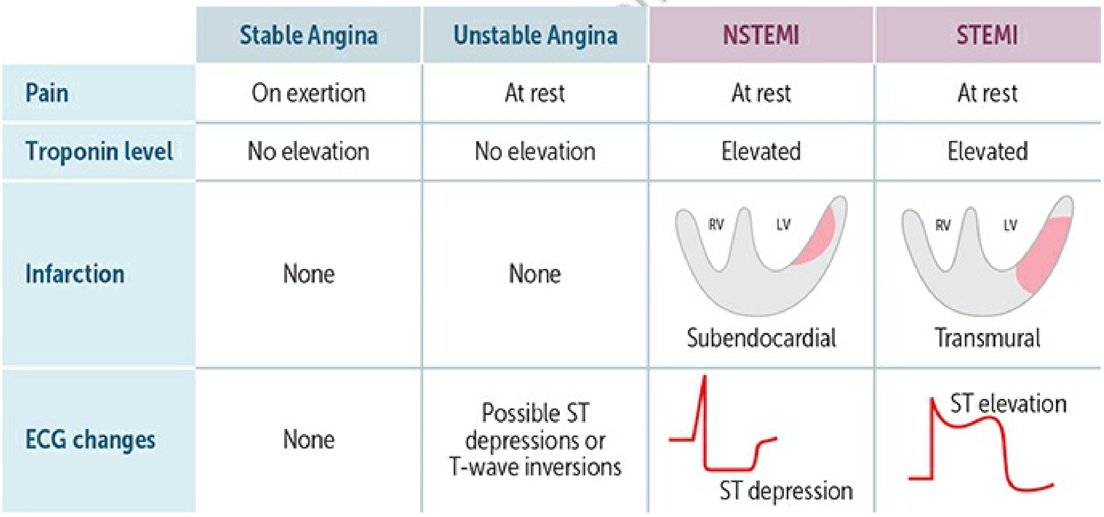
ASA and β-blockers may have mortality benefit in many patients with angina caused by coronary artery disease. However, it is important to avoid these medications if the angina is purely vasospastic (Prinzmetal angina).

ACUTE CORONARY SYNDROMES

A spectrum of clinical syndromes caused by plaque disruption or vasospasm that leads to acute myocardial ischemia.

UNSTABLE ANGINA/NON–ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Patient history and cardiac biomarkers distinguish unstable angina, stable angina, and non–ST-elevation myocardial infarction (NSTEMI). Figure 2.1-16 compares key features of stable angina, unstable angina, NSTEMI, and STEMI.



	Stable Angina	Unstable Angina	NSTEMI	STEMI
Pain	On exertion	At rest	At rest	At rest
Troponin level	No elevation	No elevation	Elevated	Elevated
Infarction	None	None	RV LV Subendocardial	RV LV Transmural
ECG changes	None	Possible ST depressions or T-wave inversions	ST depression	ST elevation

FIGURE 2.1-16. **Comparison between key features of stable angina and acute coronary syndromes (unstable angina, NSTEMI, STEMI).** (Reproduced with permission from USMLE-Rx.com.)

- **Unstable angina (UA):** Chest pain that is (1) new onset, (2) accelerating (ie, occurs with less exertion, lasts longer, or is less responsive to medications), or (3) occurs at rest suggests UA (in contrast to stable angina). Like stable angina, UA has no elevated cardiac biomarkers, suggesting myocardial ischemia without necrosis. However, unlike stable angina, UA suggests possible impending infarction due to plaque instability.
- In contrast to UA, **NSTEMI** presents with myocardial necrosis, as evidenced by elevations in troponins and creatine kinase–MB isoenzyme (CK-MB). ST-segment elevations are not seen on ECG, differentiating it from STEMI).

KEY FACT

Acute coronary syndrome:

- UA: ECG—no ST elevation; cardiac biomarkers ⊖.
- NSTEMI: ECG—no ST elevation; cardiac biomarkers ⊕.
- STEMI: ECG—ST elevation; cardiac biomarkers ⊕.

Diagnosis

- **ECG: Best initial diagnostic test.** Best initial diagnostic test. Serial ECGs should be performed (at baseline, then every 15–30 minutes initially) to identify progression to MI. UA and NSTEMI are not associated with ST elevation, but other ECG changes may be seen (eg, ST depression, T-wave inversion, nonspecific changes).
- **Cardiac markers (CK-MB/troponin):**
  - UA is not associated with elevated cardiac markers.
  - NSTEMI is associated with elevations in cardiac markers.
- **Risk stratification:** Assess mortality risk (eg, TIMI, GRACE, and HEART scores). Timing of coronary angiography ± percutaneous coronary intervention (PCI) depends on risk assessment.
- **Echocardiography** should be done routinely to assess for signs of ischemia, rule out other causes of chest pain, and assess baseline cardiac function (predictor of prognosis).

Treatment

Best initial treatment:

- **Admit to cardiac care unit (CCU)** and monitor closely.
- **Oxygen** administration if SaO_2 <90% or breathless.
- **Antiplatelet therapy:** ASA (↓ mortality in ACS) in combination with a second agent (ie, clopidogrel, prasugrel, or ticagrelor), unless contraindicated.
- **Nitrates** (IV, topical, or sublingual) for symptomatic relief of angina unless contraindicated (eg, hypotension, sildenafil use within 24 hours). IV nitrates may be used with concomitant uncontrolled HTN or HF.
- **β-blockers** should be given to all patients unless contraindicated (eg, HF, cardiogenic shock, bronchoconstriction) to reduce ischemia and mortality.
- **LMWH (eg, enoxaparin) or heparin drip** to prevent clot formation in the coronary arteries.

Interventions:

- **Immediate invasive strategy:** Immediate coronary angiography for patients who have signs of refractory angina, hemodynamic instability (HF or worsening mitral regurgitation), or electrical instability (VT/VF).
- **Early invasive strategy:** Coronary angiography within 24 hours for other high-risk patients.
- **Ischemia-guided strategy:** For low-risk patients, optimal medical therapy, with coronary angiography only in patients who develop refractory or recurrent angina, or with hemodynamic instability.

Long-term treatment:

- Dual antiplatelet therapy with aspirin and prasugrel or ticagrelor (also $P2Y_{12}$ inhibitors, but superior to clopidogrel) should be considered for up to 12 months after angioplasty and stenting to prevent in-stent thrombosis.

- Ensure patient is on long-term β-blockers (if depressed LV function), ACEIs/ARBs, and high-intensity statins.
- Address modifiable risk factors (ie, smoking, HTN, hyperlipidemia, diabetes).

KEY FACT

Initial Treatment for MI—

Oxygen – if hypoxic
ASA + additional second antiplatelet agent (NSTEMI)
Nitrates
β-blockers – unless in cardiogenic shock
Revascularization – as soon as indicated (STEMI vs NSTEMI)

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

ST-segment elevations and cardiac enzyme release secondary to prolonged cardiac ischemia and necrosis. STEMI is a common medical emergency, and prompt treatment is absolutely necessary.

History/PE

- **Presentation:** Acute-onset substernal chest pain (>10–30 min), commonly described as a pressure, tightness, or heaviness that can radiate to the left arm, shoulders, neck, or jaw. May present without chest pain (“silent” infarct).
- **Associated symptoms:** Diaphoresis (most common associated symptom), shortness of breath, lightheadedness, anxiety, nausea/vomiting, epigastric pain (more common in women), and syncope.
- **PE:** May reveal arrhythmias, hypotension (cardiogenic shock), new S_4, pansystolic murmur, and evidence of new CHF. Clear lung fields are seen in RV MI (inferior MI). In a young, otherwise healthy person, consider cocaine use as the etiology.
- **Best predictor of survival:** LVEF.

KEY FACT

It is important to check for aortic dissection clinically prior to administering anticoagulants or thrombolytics. Aortic dissection chest pain will be a tearing pain that radiates to the back along with unequal radial pulses. Initial test to assess for dissection includes a CXR, which may reveal widened mediastinum.

Diagnosis

- **ECG:** ST-segment elevations, hyperacute (tall) T waves, or new LBBB within hours (see Sgarbossa criteria in Electrocardiogram section). ST-segment depressions and dominant R waves in leads V_1–V_2 can also be a reciprocal change indicating posterior wall infarct. T-wave inversion and pathologic Q waves develop within hours to days.
  - **Sequence of ECG changes:** Peaked T waves → ST-segment elevation → Q waves → T-wave inversion → ST-segment normalization → T-wave normalization over several hours to days. Figure 2.1-4 illustrates these ECG changes over time.

- **Cardiac Enzymes:**
  - Troponin (T and I) is the most sensitive and specific cardiac marker.
  - CK-MB and the CK-MB/total CK ratio (CK index) are also regularly checked.

KEY FACT

Females, people with diabetes, older adults, and patients who have had heart transplants may have atypical or clinically silent MIs.

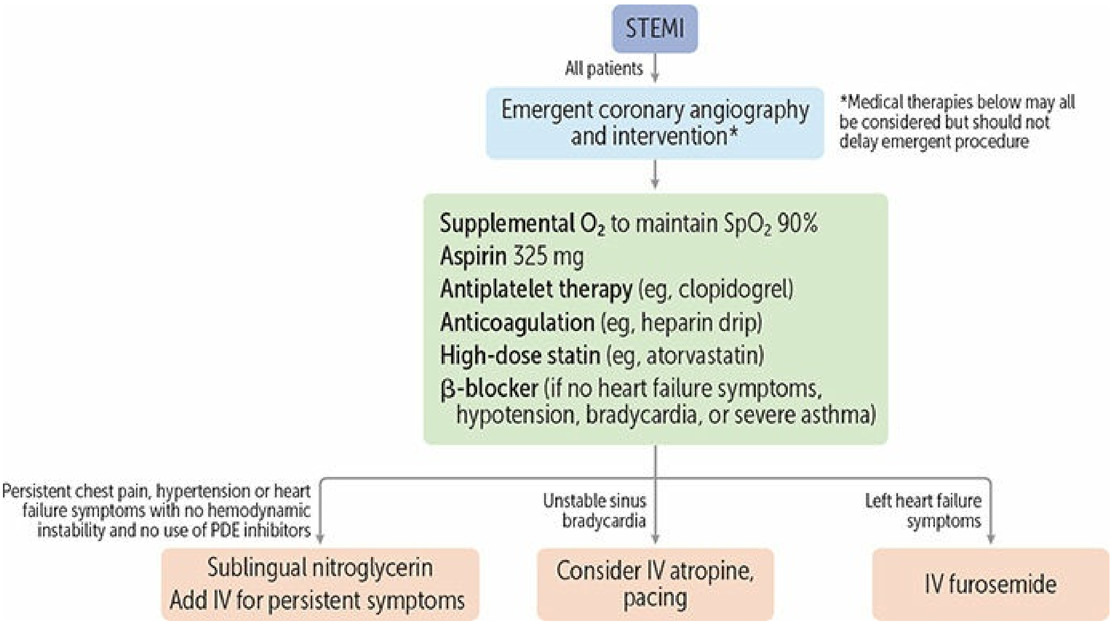

STEMI
All patients
Emergent coronary angiography and intervention*
*Medical therapies below may all be considered but should not delay emergent procedure
Supplemental O₂ to maintain SpO₂ 90%
Aspirin 325 mg
Antiplatelet therapy (eg, clopidogrel)
Anticoagulation (eg, heparin drip)
High-dose statin (eg, atorvastatin)
β-blocker (if no heart failure symptoms, hypotension, bradycardia, or severe asthma)
Persistent chest pain, hypertension or heart failure symptoms with no hemodynamic instability and no use of PDE inhibitors
Sublingual nitroglycerin
Add IV for persistent symptoms
Unstable sinus bradycardia
Consider IV atropine, pacing
Left heart failure symptoms
IV furosemide

FIGURE 2.1-17. Initial management of STEMI. *PDE*, Phosphodiesterase. (Reproduced with permission from USMLE-Rx.com.)

- Both troponin and CK-MB can take up to 3 to 12 hours to rise after the onset of chest pain. Troponin peaks at 24 to 48 hours, and CK-MB peaks within 24 hours (Fig. 2.1-18).

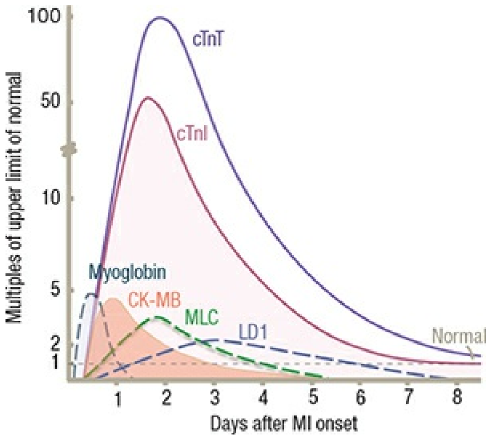


FIGURE 2.1-18. Typical pattern of serum marker elevation after an acute myocardial infarction. *CK-MB*, Creatine kinase MB isoenzyme; *cTnI*, cardiac troponin I; *cTnT*, cardiac troponin T; *LD1*, lactate dehydrogenase isoenzyme 1; *MLC*, myosin light chain. (Reproduced with permission from USMLE-Rx.com.)

- **Localization of MI based on ST-segment abnormalities:** Fig. 2.1-19 illustrates how identifying the pattern of ECG changes can be used to localize the anatomic location of STEMI. Examples are provided later.

INFARCT LOCATION	LEADS WITH ST-SEGMENT ELEVATIONS OR Q WAVES
Anteroseptal (LAD)	V_1–V_2
Anteroapical (distal LAD)	V_3–V_4
Anterolateral (LAD or LCX)	V_5–V_6
Lateral (LCX)	I, aVL
InFerior (RCA)	II, III, aVF
Posterior (PDA)	V_7–V_9, ST depression in V_1–V_3 with tall R waves

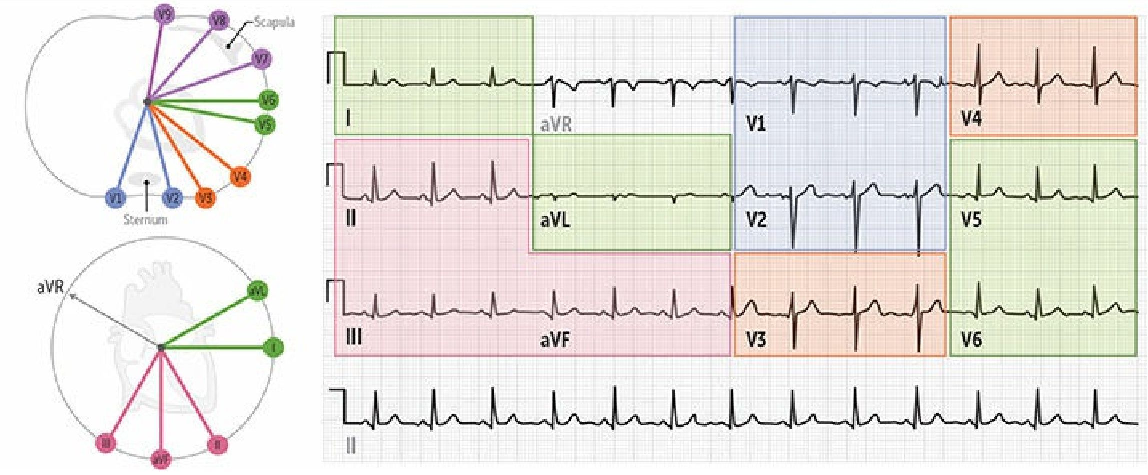

V9
V8
Scapula
V7
V6
V5
V4
V3
V2
V1
Sternum
aVR
aVL
I
II
aVF
III
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

FIGURE 2.1-19. Localization of ST elevation myocardial infarction (STEMI). (Reproduced with permission from USMLE-Rx.com.)

- **Inferior MI (involving the right coronary artery/patent ductus arteriosus [RCA/PDA]):** ST-segment elevation in leads II, III, and aVF (Fig. 2.1-20). Obtain a right-sided ECG to look for ST elevations in the RV.

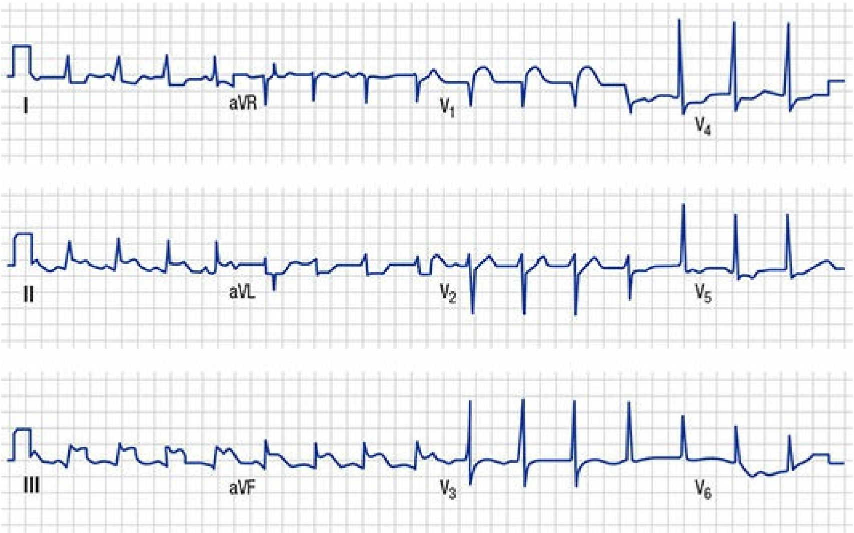

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6

FIGURE 2.1-20. Inferior wall myocardial infarction. In this patient with acute chest pain, the ECG demonstrates acute ST-segment elevation in leads II, III, and aVF with reciprocal ST-segment depression and T-wave flattening in leads I, aVL, and V_4–V_6. (Reproduced with permission from USMLE-Rx.com.)

- **Anterior MI (involving left anterior descending artery [LAD] and diagonal

branches): ST-segment elevation in leads V_1–V_4 (Fig. 2.1-21).

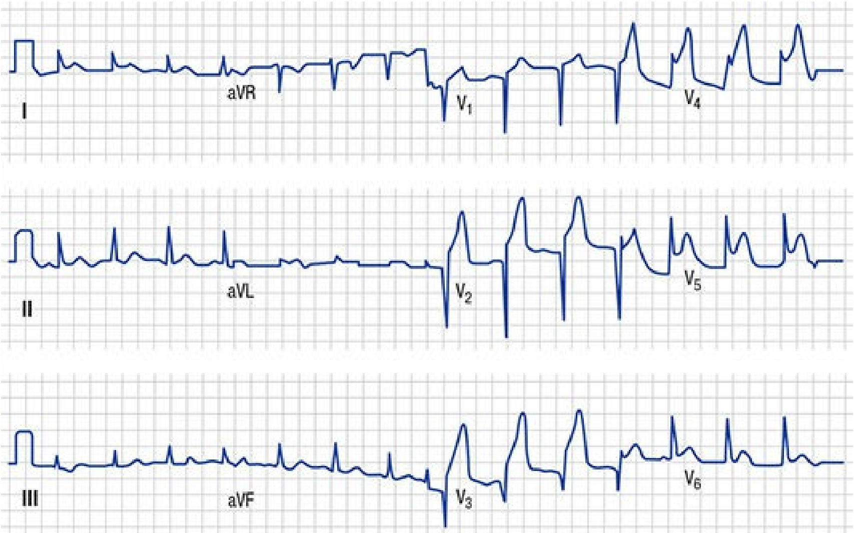


FIGURE 2.1-21. **Anterior wall myocardial infarction.** This patient presented with acute chest pain. The ECG showed acute ST-segment elevation in leads V_1–V_6 and hyperacute T waves. (Reproduced with permission from USMLE-Rx.com.)

- **Lateral MI (involving left coronary artery [LCA]):** ST-segment elevation in leads I, aVL, and V_5–V_6.
- **Posterior MI:** ST-segment depression in leads V_1–V_2 (anterior leads) can be indicative. Obtain posterior ECG leads V_7–V_9 (15-lead) to assess for ST-segment elevations.
- **Differential diagnosis:** Angina, myocarditis, pericarditis, aortic dissection, PE, esophageal reflux/spasm. These presentations are discussed in the stable angina differential diagnosis section.

Treatment

Best initial treatment: An overview of the initial management of STEMI is provided in Figure 2.1-17.

- **First line:** Antiplatelet therapy; ASA (↓ mortality in ACS) + P2Y12 inhibitor (prasugrel or ticagrelor if PCI planned [superior to clopidogrel]; if undergoing fibrinolysis, clopidogrel is used [prasugrel/ticagrelor relatively contraindicated]).
- **Nitrates** (IV, topical, or sublingual): For symptomatic relief of angina unless contraindicated (eg, hypotension, sildenafil used within 24 hours). IV nitrates may be used with concomitant uncontrolled HTN or HF.
- If SaO_2 <90% to 92%, breathless, or in acute LVF, administer O_2.
- β-blockers should be given to all patients unless contraindicated (eg, HF, cardiogenic shock, bronchoconstriction) to reduce ischemia and mortality.
- If the patient is in HF or in cardiogenic shock, do not give β-blockers. Consider ACEIs in HF provided that the patient is not hypotensive.
- In inferior wall MI (ie, RV infarction), avoid nitrates and diuretics due to risk for severe hypotension (preload dependent). IV fluids can improve hemodynamics by increasing preload.

KEY FACT

Summary of ACS medical management:

- UA: No ST elevation; cardia biomarkers ⊖. Tx: Aspirin.
- NSTEMI: No ST elevation; cardiac biomarkers ⊕. Tx: Aspirin, clopidogrel/ticagrelor, and LMWH or heparin drip.
- For both UA and NSTEMI: Tx: Nitrates and β-blockers if not hypotensive.
- STEMI: ST elevation; cardiac biomarkers ⊕. Tx: Angioplasty with stent placement.

Interventions:

- Emergent angiography and PCI should be performed if possible (superior to thrombolysis).
- If PCI cannot be performed <120 minutes (door-to-balloon time should ideally be <90 minutes), and there are no contraindications to thrombolysis, thrombolysis with alteplase (tPA), reteplase, or streptokinase should be performed instead of PCI.
- Although thrombolysis should be performed within 3 hours of chest pain onset, it can be used up to 12 hours from the onset of symptoms (mortality benefit extends to 12 hours). Thrombolysis is contraindicated if >24 hours.

KEY FACT

Contraindications to thrombolysis:

- Previous intracranial hemorrhage or major GI bleed.
- Recent major trauma/surgery/head injury.
- Ischemic stroke within the last 6 months.
- Severe hypertension (>180/110 mm Hg).
- Known bleeding disorder.

Long-term treatment:

- Long-term management for all patients includes ASA, ACEIs, β-blockers, nitrates, and high-dose statins.
- After PCI is performed, dual antiplatelet therapy (aspirin and a P2Y12 receptor blocker, eg, clopidogrel, prasugrel, ticagrelor) is necessary:
  - If bare metal stent is placed, >30 days of dual antiplatelet therapy is necessary.
  - If drug-eluting stent is placed, >12 months of dual antiplatelet therapy is necessary.
- Address modifiable risk factors (eg, smoking, HTN, hyperlipidemia, diabetes).

KEY FACT

Indications for coronary artery bypass graft surgery (CABG):

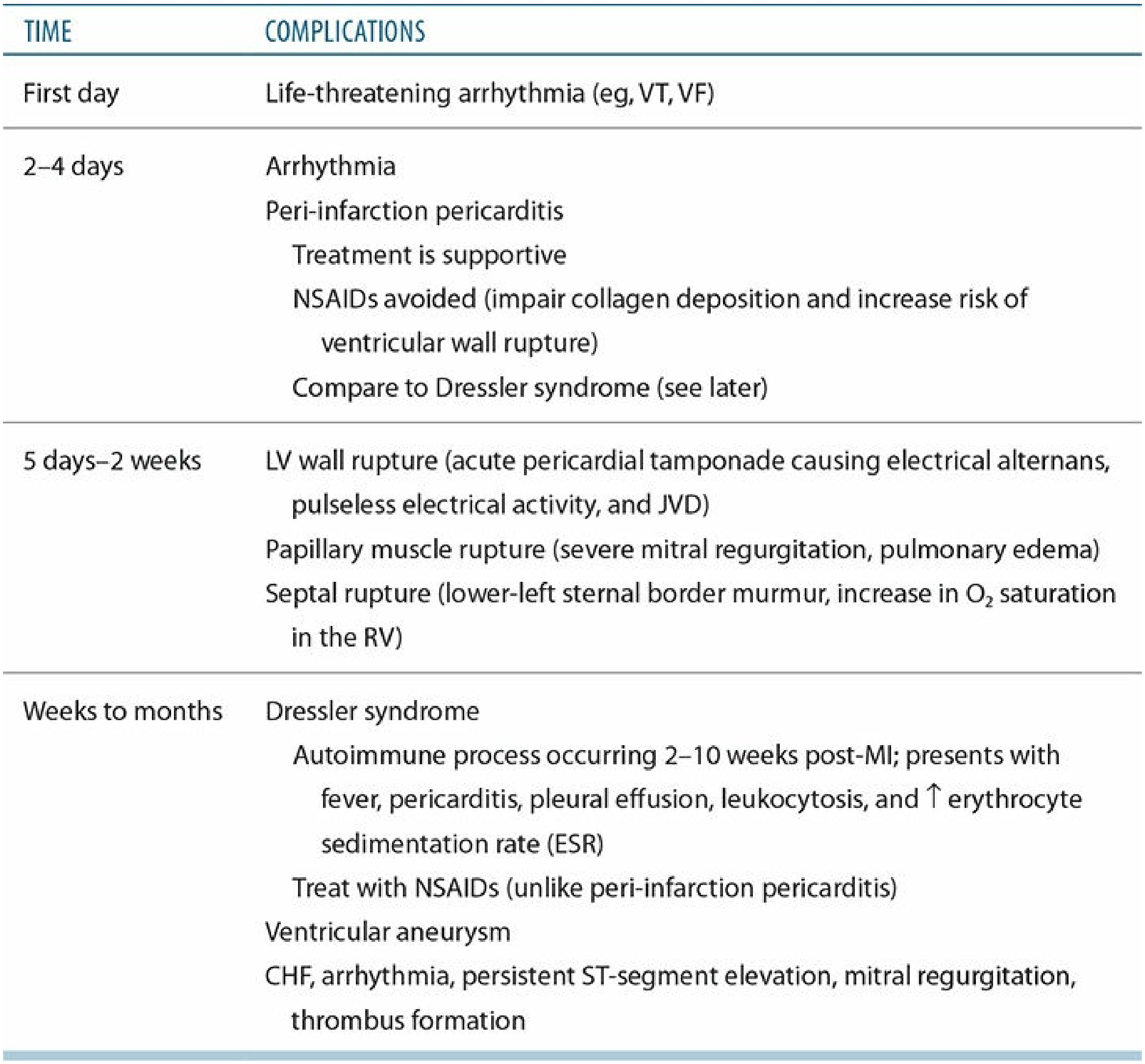
- Left main CAD.
- Triple-vessel disease with ≥70% in each vessel.
- Two-vessel disease in diabetic patient.
- Symptomatic patient despite maximal medical therapy.
- Coronary obstruction not amenable to PCI.

Complications

- **Arrhythmia:** VF and VT are the most common complications and the most common causes of sudden death after acute MI. Sinus bradycardia and third-degree (complete) heart block are also very common.

- Less common complications include reinfarction, LV wall rupture, VSD, pericarditis, papillary muscle rupture (with mitral regurgitation), LV aneurysm or pseudoaneurysm, and mural thrombi (with subsequent acute limb ischemia, TIA, or stroke).
- Complications noted earlier tend to occur at different times in the course of this disease. This is detailed in Table 2.1-16.

TABLE 2.1-16. A Timeline of Common Post-MI Complications



TIME	COMPLICATIONS
First day	Life-threatening arrhythmia (eg, VT, VF)
2–4 days	Arrhythmia Peri-infarction pericarditis Treatment is supportive NSAIDs avoided (impair collagen deposition and increase risk of ventricular wall rupture) Compare to Dressler syndrome (see later)
5 days–2 weeks	LV wall rupture (acute pericardial tamponade causing electrical alternans, pulseless electrical activity, and JVD) Papillary muscle rupture (severe mitral regurgitation, pulmonary edema) Septal rupture (lower-left sternal border murmur, increase in O_2 saturation in the RV)
Weeks to months	Dressler syndrome Autoimmune process occurring 2–10 weeks post-MI; presents with fever, pericarditis, pleural effusion, leukocytosis, and ↑ erythrocyte sedimentation rate (ESR) Treat with NSAIDs (unlike peri-infarction pericarditis) Ventricular aneurysm CHF, arrhythmia, persistent ST-segment elevation, mitral regurgitation, thrombus formation

- **RV infarction:** Caused by occlusion of the RCA. Presents with hypotension, JVD, and clear lungs. Treat with revascularization and volume replacement (preload dependent). Avoid nitrates and diuretics.

KEY FACT

RV MI is caused by occlusion of the RCA. As dysfunctional RV is dependent on preload to maintain stroke volume, preload-reducing drugs (nitrates and diuretics) can cause severe hypotension and must be avoided. In RV MI with shock, treat with IV fluids to optimize preload, and add inotropes if necessary.

CAROTID ARTERY STENOSIS

Atherosclerotic lesion of either or both carotid arteries. Accounts for 20% of TIAs and embolic strokes.

History/PE

- Often asymptomatic.
- Symptomatic disease is characterized by sudden-onset focal neurologic defect in the past 6 months (ie, TIA or stroke).
- PE may reveal carotid artery bruit.
- **Risk factors:** Advanced age, smoking, HTN, hyperlipidemia, diabetes, obesity, and family history of CAD and/or carotid artery disease.

Diagnosis

Duplex ultrasonography can determine percent occlusion.

Treatment

- **Definitive treatment:** Carotid endarterectomy (CEA). Carotid stenting in some select cases.
- CEA recommended in symptomatic (TIA/stroke in last 6 months) patients with 70% to 99% stenosis.
- Based on procedural risk and patient factors (eg, age, sex, comorbidities, life expectancy), consider in symptomatic patients with 50% to 69% or asymptomatic with 60% to 99% stenosis.
- With 100% blockage, CEA or stenting is contraindicated (there can be no thromboembolism from a completely occluded vessel).

DYSLIPIDEMIA

- Increased total cholesterol, LDL-C, or triglyceride levels or decreased HDL levels. Although these are all risk factors for atherosclerotic cardiovascular disease (ASCVD; ie, CAD, stroke), LDL-C is the dominant atherogenic cholesterol.
- Dyslipidemia may be due to primary (genetic conditions such as familial combined hypercholesterolemia or familial hypertriglyceridemia) or secondary causes.
- Secondary causes include DM, cholestatic liver disease, nephrotic syndrome, chronic renal disease, hypothyroidism, obesity, cigarette smoking, excessive alcohol consumption, and certain medications (eg, thiazide diuretics, β-blockers, oral contraceptive pills [OCPs], clozapine). Optimizing treatment of secondary causes is indicated in all patients.

History/PE

- Most patients have no specific signs or symptoms.
- Patients with extremely high triglyceride or LDL levels may have xanthomata (eruptive itchy nodules, orange streaks in palmar creases, or tuberous plaques on the elbows and knees); xanthelasma (yellow fatty deposits in the skin around the lids just below the eyes); lipemia retinalis (creamy appearance of retinal vessels); or corneal arcus (deposition of lipid in the corneal stroma).
- Patients with very high triglyceride levels (>500 mg/dL) may initially present with

pancreatitis.

- Patients may have a history of primary familial hyperlipidemias.

KEY FACT

Causes of secondary hyperlipidemia include Cushing syndrome, hypothyroidism, nephrotic syndrome, and cholestasis.

Diagnosis

- **Best initial test:** Lipid profile may show ↑ total cholesterol, ↑ LDL-C, ↑ triglycerides, or ↓ HDL.
- **Indications for testing:** Screen all patients >35 years of age or those ≥20 years of age with risk factors for ASCVD and repeat every 5 years or sooner if lipid levels are elevated. Additionally, smokers of all ages should be screened for dyslipidemias due to their ↑ risk.
- **Interpretation of results:**
  - Risk of ASCVD: 10-year risk of ASCVD, estimated using the Pooled Cohort Equations tool, directs further treatment.
  - Individuals with LDL >190 mg/dL, triglycerides ≥500 mg/dL, family history of premature atherosclerotic disease, or physical signs of dyslipidemia (eg, tendon xanthoma) should also be evaluated for primary causes of hyperlipidemia.

KEY FACT

As you cannot calculate the patient's ASCVD risk on the USMLE, focus on obvious signs of ↑ risk (smoking, diabetes) or ↓ risk (young, healthy) when deciding if statin therapy is appropriate.

Treatment

Elevated LDL-C: Lowering LDL-C may reduce the risk of ASCVD.

- **Lifestyle therapies:** Dietary modification (eg, low fat, reduced red meat, increased fiber), aerobic exercise, and weight loss are recommended in all patients.
- **Indications for pharmacotherapy:** The American College of Cardiology/American Heart Association recommendations are presented in Table 2.1-17.

TABLE 2.1-17. **American College of Cardiology/American Heart Association Treatment Guidelines for Management of Hyperlipidemia**

PATIENT AGE	CRITERIA	TREATMENTS IN ADDITION TO LIFESTYLE
All ages	Atherosclerotic cardiovascular disease (ASCVD, eg, CAD, cerebrovascular accident, or peripheral artery disease)	High-intensity statin ± ezetimibe Very high risk: Add PCSK9 inhibitors if required
20–75 years	LDL-C ≥190 mg/dL, without ASCVD	High-intensity statin
20–39 years	Family history of premature ASCVD and LDL-C ≥160 mg/dL, without ASCVD	Consider statin
40–75 years	Type DM, without ASCVD	Moderate-intensity or high-intensity statin based on risk
40–75 years	LDL-C 70–189 mg/dL with diabetes; LDL-C 70–189 mg/dL, without type 2 DM or ASCVD	5%–7.5% 10-year risk: moderate-intensity statin 7.5%–19% 10-year risk: moderate-intensity statin ≥20% 10-year risk: high-intensity statin
>75 years	No ASCVD, regardless of LDL-C	Clinical assessment and risk discussion

- Statins are the initial drug of choice for the treatment of hypercholesterolemia. Commonly used lipid-lowering agents are listed in Table 2.1-18.

TABLE 2.1-18. Lipid-Lowering Agents

CLASS	EXAMPLES	EFFECT ON LIPID PROFILE	ADVERSE EFFECTS
HMG-CoA reductase inhibitors (statins)	Atorvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin	↓ LDL, ↓ triglycerides	↑ LFTs, myositis, warfarin potentiation
Lipoprotein lipase stimulators (fibrates)	Gemfibrozil	↓ triglycerides, ↑ HDL	GI upset, cholelithiasis, myositis (especially in combination with statins), ↑ LFTs, pancreatitis
Cholesterol absorption inhibitors	Ezetimibe	↓ LDL	Diarrhea, abdominal pain; can cause angioedema
Niacin	Niaspan	↑ HDL, ↓ LDL	Skin flushing (can be prevented with ASA, due to ↑ prostaglandins), paresthesias, pruritus, GI upset, ↑ LFTs
Bile acid resins	Cholestyramine, colestipol, colesevelam	↓ LDL	Constipation, GI upset, LFT abnormalities, myalgias; can ↓ absorption of other drugs from the small intestine
Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors	Evolocumab, alirocumab (injectable medications taken every 2–4 weeks)	↓↓ LDL	Injection-site swelling, rash, muscle/limb pain, backache

- **Intensity of therapy:** Medication regimen varies based on the goal LDL reduction. High-intensity statin therapy (eg, atorvastatin 40 and 80 mg or rosuvastatin 20 and 40 mg) reduces LDL-C >50%, while moderate-intensity therapy lowers LDL-C by 30%–50%.

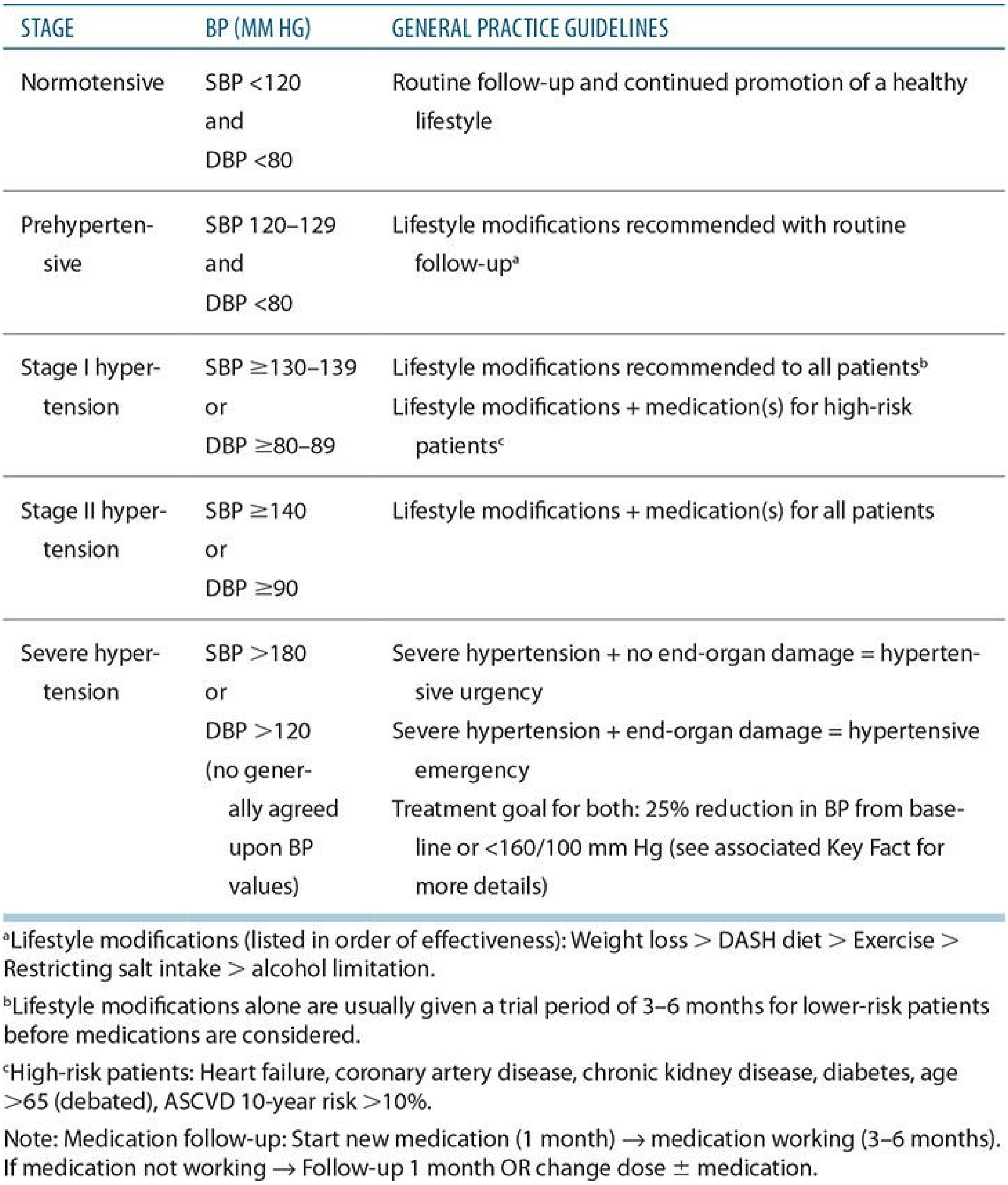
Elevated triglycerides:

- **Initial treatment:** Lifestyle therapies (diet, exercise, weight loss), treatment of secondary causes (eg, optimization of chronic kidney disease [CKD] or diabetes therapy), and avoidance of medications that may cause hypertriglyceridemia.
- If ASCVD risk ≥7.5% after initial treatment, statins may be considered.
- **Prevention of pancreatitis:** Patients with severe hypertriglyceridemia (especially triglycerides ≥1000 mg/dL) benefit from fibrate therapy to prevent pancreatitis.

HYPERTENSION

HTN is the most common disease in the United States and the key risk factor in MI and stroke. Stage 1 HTN is defined as an SBP ≥130 to 139 mm Hg or a diastolic blood pressure (DBP) ≥80 to 89 mm Hg. Measurements are based on an average of ≥2 readings obtained on ≥2 occasions separated in time in adults (see Table 2.1-19 for classifications). HTN is classified as primary or essential without an identifiable cause and secondary when an identifiable cause exists.

TABLE 2.1-19. Definitions of Blood Pressure Values for Adults (>18 years) and General Practice Guidelines



STAGE	BP (MM HG)	GENERAL PRACTICE GUIDELINES
Normotensive	SBP <120 and DBP <80	Routine follow-up and continued promotion of a healthy lifestyle
Prehypertensive	SBP 120–129 and DBP <80	Lifestyle modifications recommended with routine follow-up[a]
Stage I hypertension	SBP ≥130–139 or DBP ≥80–89	Lifestyle modifications recommended to all patients[b] Lifestyle modifications + medication(s) for high-risk patients[c]
Stage II hypertension	SBP ≥140 or DBP ≥90	Lifestyle modifications + medication(s) for all patients
Severe hypertension	SBP >180 or DBP >120 (no generally agreed upon BP values)	Severe hypertension + no end-organ damage = hypertensive urgency Severe hypertension + end-organ damage = hypertensive emergency Treatment goal for both: 25% reduction in BP from baseline or <160/100 mm Hg (see associated Key Fact for more details)

[a] Lifestyle modifications (listed in order of effectiveness): Weight loss > DASH diet > Exercise > Restricting salt intake > alcohol limitation.

[b] Lifestyle modifications alone are usually given a trial period of 3–6 months for lower-risk patients before medications are considered.

[c] High-risk patients: Heart failure, coronary artery disease, chronic kidney disease, diabetes, age >65 (debated), ASCVD 10-year risk >10%.

Note: Medication follow-up: Start new medication (1 month) → medication working (3–6 months). If medication not working → Follow-up 1 month OR change dose ± medication.

PRIMARY (ESSENTIAL) HYPERTENSION

Hypertension that has no identifiable cause and represents ~95% of cases.

KEY FACT

PCSK9 inhibitors are a new class of LDL-lowering drugs. They significantly increase hepatic clearance of LDL. Indicated in familial hypercholesterolemia and statin-resistant or statin-intolerant patients with severe hyperlipidemia.

Risk factors:

- Nonmodifiable: Increasing age, male sex, Black race, family history.
- Modifiable: High-salt diet, alcohol (amount varies), obesity, sedentary lifestyle.

History/PE/Complications

- Majority of patients are asymptomatic (“silent killer”) and found on routine screening.
- Symptomatic patients exhibit end-organ damage as HTN ↑ atherosclerosis + ↑ arteriosclerosis:
  - **Eyes:** Early (AV nicking, cotton wool spots) → later (hemorrhage, exudates, papilledema). See Figure 2.1-22.

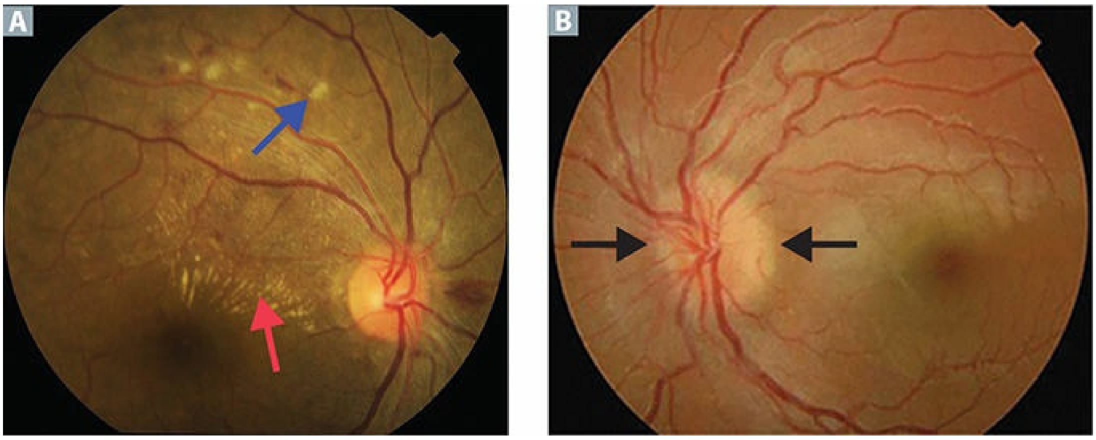


FIGURE 2.1-22. **Hypertensive retinopathy. (A)** Cotton wool spots *(blue arow)* and hard exudates *(red arrow)*. **(B)** Papilledema *(black arrows)*. (Adapted with permission from Diallo JW, Méda N, Tougouma SJ, et al. Intérêts de l’examen du fond d’œil en pratique de ville: bilan de 438 cas [Interests of the examination of the fundus in general practice: review of 438 cases]. *Pan Afr Med.* 2015;20. doi:10.11604/pamj.2015.20.363.6629. B: Adapted with permission Kanonidou E, Chatziralli I, Kanonidou C, Parava M, Ziakas N. Unilateral optic disc edema in a paediatric patient: Diagnostic dilemmas and management. Case Rep Med. 2010;2010:529081. doi:10.1155/2010/529081.).

  - **Central nervous system (CNS):** Encephalopathy, stroke (intracerebral hemorrhage, lacunar, ischemic, TIAs).
  - **Cardiovascular:** CAD → MI, LV hypertrophy → CHF, peripheral arterial disease (PAD), aortic aneurysms/dissections.
  - **Kidney:** Arteriosclerosis of glomerulus → nephrosclerosis, ↓ GFR/dysfunctional tubules → failure. See Figure 2.1-23.

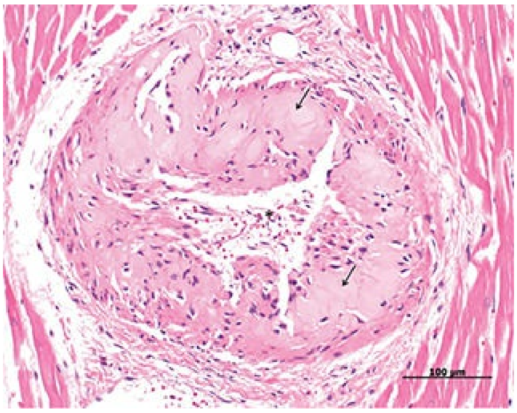


FIGURE 2.1-23. Hyaline arteriolosclerosis occurs secondary to plasma protein leakage into the endothelium due to essential hypertension or diabetes mellitus. (Reproduced with permission from Sostaric-Zuckermann IC, Borel N, Kaiser C, et al. Chlamydia in canine or feline coronary arteriosclerotic lesions. *BMC Res Notes*. 2011;4:350. doi: 10.1186/1756-0500-4-350.)

Diagnosis

- **Measurement:** Never diagnose HTN on one reading unless severe HTN or end-organ damage is present. Measurements are based on an average of ≥2 readings obtained on ≥2 occasions separated in time (days, weeks) in adults. **Ambulatory BP monitoring is the gold standard.** Ambulatory BP and outpatient BP (with home BP monitors) monitoring help exclude white coat hypertension (elevated BP only in clinic) as a cause of HTN. Serial clinic BP checks can also be used.
- **New-onset HTN:** Once primary HTN is diagnosed, the next best step is to **screen for complications and comorbid conditions,** which include HbA1c or fasting glucose, lipid panel, chemistry panel (serum Cr, blood urea nitrogen [BUN], K), ECG (screen for LV hypertrophy, Q waves for previous MI), and a urinalysis (protein).
- **Secondary cause of HTN:** If suspected, order appropriate tests (see secondary HTN key fact).

Treatment

- **Best initial treatment:** Lifestyle modifications listed in order of effectiveness: **Weight loss** (in overweight people) > **DASH diet** > exercise > restricting salt intake > alcohol limitation (if patient has refractory HTN, limiting alcohol may be the answer). Depending on patient, usually tried for 3 to 6 months before drugs are considered.
- **Best initial medications:** Choice of thiazide diuretics (usually), ACEs/ARBs, or dihydropyridine CCBs unless a compelling indication exists (Tables 2.1-20 and 2.1-21).

TABLE 2.1-20. Compelling Indications for Treatment of Primary Hypertension

IF HISTORY OF . . .	. . . THEN BEST INITIAL TREATMENT(S)
Prior myocardial infarction, coronary artery disease, compensated heart failure, atrial fibrillation, hyperthyroidism	β-blockers are a high-yield answer for exams + practice (others may include CCBs, ACE/ARBs, diuretics, and aldosterone antagonists, *depending on condition*)
CKD, proteinuria, diabetes	ACEIs or ARBs (renal protective in diabetics)
Benign prostatic hyperplasia	α-Blockers → smooth muscle relaxation of blood vessels (vasodilation) + bladder/prostrate
Osteoporosis Black race[a]	Thiazides → blocks Na-Cl reabsorption in DCT →↑ calcium reabsorption
Current pregnancy	"**He** **Li**kes **My** **N**eonate" **H**ydralazine, **L**abetalol (use first), **M**ethyldopa, **N**ifedipine
Asthma	ARBs (NOT ACEIs because bradykinin → cough), CCBs, thiazide diuretics, cardioselective (β_1) β-blockers

[a] Controversial "salt-sensitive HTN" in Black individuals. CCBs are equally first line.

TABLE 2.1-21 Major Classes of Antihypertensive Agents, Mechanism of Actions, and Adverse Effects

CLASS	AGENTS	MECHANISM OF ACTION	ADVERSE EFFECTS
Thiazide diuretics	Hydrochloro**thiazide,** chlorthalidone, metolazone. "Thiazides get it **done** = chlorthali**done**." "Get in the **zone** with a thiazide = metola**zone**."	Thiazides → block Na^+/Cl^- reabsorption in DCT → Na^+/H_2O excretion → ↓ BP.	Elevate blood levels (hyper**GLUC**) of **G**lucose, **L**ipids, **U**ric acid, **C**alcium. So, caution use in diabetes, ↑TGs, ↑ uric acid → gout, hypercalcemia. Causes metabolic alkalosis, ↓ K+, can lead to hyponatremia (promotes Na^+ loss with no change to medullary gradients' osmolarity that drive H_2O reabsorption → if patient ↑ H_2O intake → hyponatremia).
Loop diuretics	Sulfonamides: furosemide, torsemide, bumetanide. Non-sulfonamide: ethacrynic acid.	**Loops** → block $Na^+/K^+/2Cl^-$ pump in thick ascending **loop** of Henle → ↓ medullary osmotic gradients → ↑↑↑ Na^+/H_2O excretion → ↓ BP.	Metabolic alkalosis, ↓ K^+, ↓ Ca^{2+}, ↓ Mg^{2+}, ↑ uric acid → gout, ototoxicity (all + ↑ ↑ risk ethacrynic acid). "Loop earrings hurt your ears." Sulfonamides → rash + acute interstitial nephritis.

CLASS	AGENTS	MECHANISM OF ACTION	ADVERSE EFFECTS
K^+-sparing diuretics	**S**pironolactone, **T**riamterene, **E**plerenone, **A**miloride, **K**$^+$-sparing = **STEAK**.	Spironolac**tone** + epleren**one** → aldo**sterone**-R inhibitors. Triamterene + amiloride → inhibit epithelial Na^+ channels.	Hyperkalemia + metabolic acidosis. Spironolactone mimics/blocks testosterone + progesterone effects → gynecomastia (men) + amenorrhea (women).
β-blockers	Cardioselective (β_1- > β_2-blockers) are mostly in ***first*** part of alphabet **(A–M):** **A**tenolol, **A**cebutolol (partial agonist), **B**etaxolol, **B**isoprolol, **E**smolol, **M**etoprolol (“**ABEAM**”). **N**on-**Z**elective ($\beta_1 = \beta_2$ blockers) are mostly in ***second*** part of alphabet **(N–Z):** **N**adolol, **P**indolol (partial agonist), **P**ropranolol, **T**imolol. Nonselective β- and α-blockers ($\beta_1 = \beta_2 \geq \alpha_1 > \alpha_2$) have a modified suffix (instead of “-olol”): carved**ilol**, labet**alol**.	Block β_1 on heart + kidney → ↓ HR, cardiac contractility, renin release → ↓ effective circulating volume, CO → ↓ BP. Block β_2 on lungs + liver → bronchoconstriction + ↓ portal blood flow (useful to treat portal hypertension in cirrhosis patients).	Caution in obstructive lung diseases (nonselective agents → bronchospasm), decompensated HF (↓ mortality in compensated HF), heart block (block β_1 → bradycardia), diabetes (commonly used but can mask hypoglycemia), depression. Sleep disturbances (insomnia), fatigue, erectile dysfunction, ↓ HDL, ↑ TGs. Overdose treatment: glucagon.
ACEIs + ARBs + related agents	ACEIs: end in **pril** (lisino**pril**, capto**pril**). Please celebrate **April** as national ACEI month. ARBs: end in **sartan** (losartan, valsartan). Entresto = valsartan/sacubitril (inhibits neprilysin). Aliskiren = direct renin inhibitor.	ACEI: inhibit angiotensin I → angiotensin II conversion = vasodilation + ↓ aldosterone → ↑ Na^+/H_2O excretion → ↓ BP. ARBs: inhibit angiotensin II receptor → same as earlier. Neprilysin inhibition → ↑ angiotensin II (pair w/ ARB) + ↑ natriuretic peptides (A/BNP). Aliskiren inhibits renin → ↓ angiotensinogen conversion → angiotensin I → ↓ angiotensin II + aldosterone → diuresis + ↓ BP.	ACEI → ↑ bradykinin → cough + angioedema. ARBs have less risk. ACEI, ARBs, Aliskiren → ↓ GFR (acute renal failure) as efferent arteriole vasoconstriction controlled by angiotensin II. ↓ aldosterone → ↑ K^+. Renal teratogens, cause rash. *Entresto's main side effects = ARBs.
CCBs	Dihydropy**ridine** CCBs (amlod**ipine**, nifed**ipine**) = more selective for vascular smooth muscle. Nondihydropyridine CCBs (diltiazem, verapamil) = more selective for cardiac muscle.	Block voltage-dependent L-type Ca^{2+} channels in cardiac (↓ HR, contractility) + vascular smooth muscle (↓ BP) to varying degrees.	Gingival hyperplasia. Dihydropyridines → vasodilation → headache, flushing, peripheral edema, reflex tachycardia (may coadminister β-blocker). Nondihydropyridines: ⊖ inotropes → precipitate HF, AV block, ↓ HR/contractility, verapamil (constipation, ↑ prolactin).

CLASS	AGENTS	MECHANISM OF ACTION	ADVERSE EFFECTS
α_1-Antagonists	Common **-osin** suffix: prazo**sin**, doxazo**sin**, terazo**sin**, alfuzo**sin**, tamsulo**sin**.	Block α_1 → inhibits smooth muscle contraction in vasculature (↓ BP) + bladder/prostate (↑ urine flow).	Although any anti-HTN agent can cause postural hypotension, these agents are notorious. Headache, dizziness, reflex tachycardia (may coadminister β-blocker). Tamsulosin = uroselective = less ↓ BP.
α_2-Agonists	Methyldopa (a drug of choice in pregnancy), clonidine.	Stimulate presynaptic CNS α_2 receptors → ⊖ feedback → ↓ norepinephrine → ↓ BP.	Clonidine → ↓ sympathetic response → somnolence, ↓ HR, ↓ respirations, miosis. Dry mouth and severe rebound HTN with sudden dose stoppage → ↑↑↑ sympathetic response. Methyldopa: direct Coombs ⊕ warm autoimmune hemolytic anemia, sedation, drug-induced lupus (⊕), anti-histone Abs, hyperprolactinemia.
Vasodilators	Hydralazine (a drug of choice in pregnancy), minoxidil.	Hydralazine → ↑ NO → ↑ cGMP → arteriolar vasodilation (↓ BP). Minoxidil → opens K$^+$ channels → vasodilation (↓ BP).	Hydralazine: drug-induced lupus ⊕ anti-histone Abs, fluid retention, reflex tachycardia (may coadminister β-blocker). Minoxidil = rogaine = hypertrichosis.
Hypertensive emergency agents	β-blockers (labetalol or esmolol), CCBs (clevidipine or nicardipine), hydralazine, enalapril, nitroprusside and fenoldopam (explained here).	Nitroprusside → ↑ NO → ↑ cGMP → vein/arteries dilate → ↓ BP. Fenoldopam D1 agonist, arteries dilate, especially in kidneys → maintenance renal perfusion + ↑ Na$^+$/H_2O excretion → ↓ BP.	Nitroprusside prolonged use → cyanide poisoning → inhibition ETC → severe lactic acidosis. Fenoldopam → vasodilation → headache, flushing, nausea.

- **General management goals:** BP should be lowered to <130/80 mm Hg in most patients with hypertension as tolerated. Although 70% of patients are controlled with one drug, 90% are controlled with two to three drugs. For example, if a thiazide diuretic alone doesn't control HTN, consider adding an ACEI/ARB, a CCB, or a β-blocker (depending on the patient/compelling indications).

MNEMONIC

Initial Drug Treatment of HTN—

TAC

T (Thiazide diuretics usually initial choice)
ACEIs/**A**RBs
CCBs

Q

A patient is diagnosed with new-onset primary HTN. The physician recommends lifestyle modifications with a focus on weight loss, with follow-up scheduled 3 months later to evaluate the need for medications. What is the next best step in evaluating this patient?

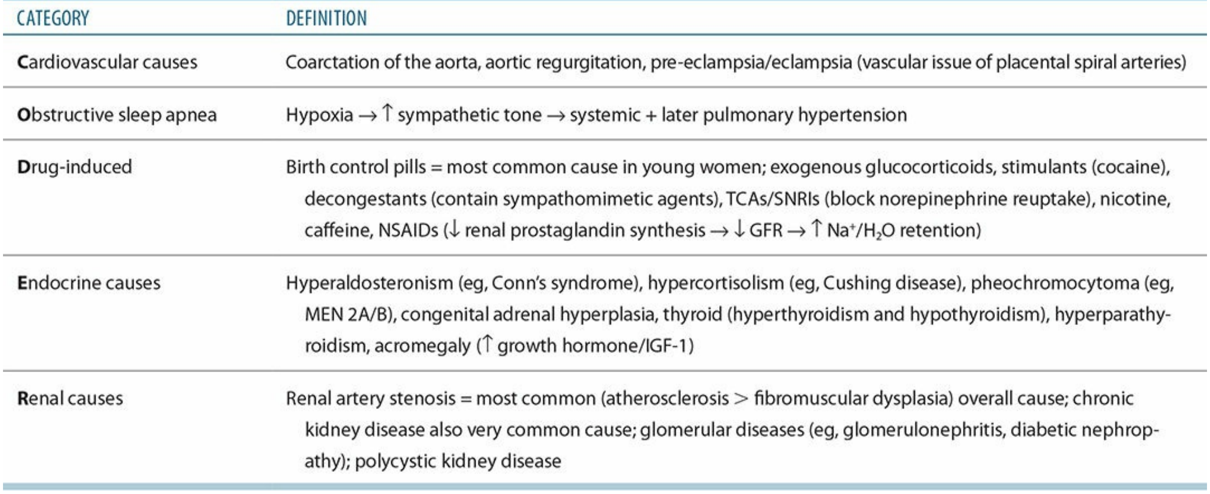
A

Once primary HTN is diagnosed, the next best step is to screen for complications and comorbid conditions, which include HbA1c or fasting glucose, lipid panel, chemistry panel (serum Cr, BUN, K), ECG (screen for LV hypertrophy, Q waves for previous MI), and a urinalysis (protein).

SECONDARY HYPERTENSION

HTN that occurs secondary to an identifiable cause (see Table 2.1-22). Identifiable causes of HTN account for a minority (~5%) of cases. Patients should be worked up for secondary causes of HTN if they are younger (age <35), have a severely elevated or refractory-to-treatment BP, or a specific sign indicating a secondary cause.

TABLE 2.1-22. **Subset of Identifiable Causes of Secondary Hypertension**



CATEGORY	DEFINITION
Cardiovascular causes	Coarctation of the aorta, aortic regurgitation, pre-eclampsia/eclampsia (vascular issue of placental spiral arteries)
Obstructive sleep apnea	Hypoxia → ↑ sympathetic tone → systemic + later pulmonary hypertension
Drug-induced	Birth control pills = most common cause in young women; exogenous glucocorticoids, stimulants (cocaine), decongestants (contain sympathomimetic agents), TCAs/SNRIs (block norepinephrine reuptake), nicotine, caffeine, NSAIDs (↓ renal prostaglandin synthesis → ↓ GFR → ↑ Na^+/H_2O retention)
Endocrine causes	Hyperaldosteronism (eg, Conn's syndrome), hypercortisolism (eg, Cushing disease), pheochromocytoma (eg, MEN 2A/B), congenital adrenal hyperplasia, thyroid (hyperthyroidism and hypothyroidism), hyperparathyroidism, acromegaly (↑ growth hormone/IGF-1)
Renal causes	Renal artery stenosis = most common (atherosclerosis > fibromuscular dysplasia) overall cause; chronic kidney disease also very common cause; glomerular diseases (eg, glomerulonephritis, diabetic nephropathy); polycystic kidney disease

MNEMONIC

Causes of secondary hypertension

CODER

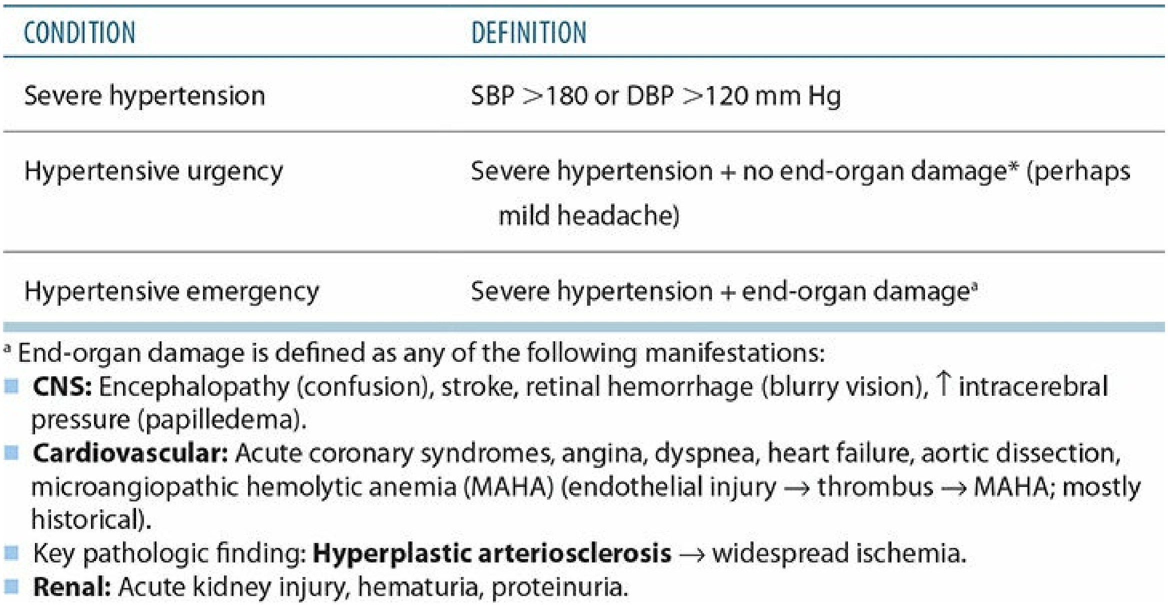
Cardiovascular cause
Obstructive sleep apnea
Drug induced
Endocrine causes
Renal causes

HYPERTENSIVE EMERGENCY/URGENCY

Presentation

The features of severe HTN, hypertensive urgency, and emergency are compared in Table 2.1-23.

TABLE 2.1-23. **Presentation of Hypertensive Urgency and Emergency**



CONDITION	DEFINITION
Severe hypertension	SBP >180 or DBP >120 mm Hg
Hypertensive urgency	Severe hypertension + no end-organ damage* (perhaps mild headache)
Hypertensive emergency	Severe hypertension + end-organ damage[a]

[a] End-organ damage is defined as any of the following manifestations:
- **CNS:** Encephalopathy (confusion), stroke, retinal hemorrhage (blurry vision), ↑ intracerebral pressure (papilledema).
- **Cardiovascular:** Acute coronary syndromes, angina, dyspnea, heart failure, aortic dissection, microangiopathic hemolytic anemia (MAHA) (endothelial injury → thrombus → MAHA; mostly historical).
- Key pathologic finding: **Hyperplastic arteriosclerosis** → widespread ischemia.
- **Renal:** Acute kidney injury, hematuria, proteinuria.

Treatment

Goal: A 25% reduction in BP from baseline or <160/100 mm Hg for both hypertensive urgency and emergency. Medications: eg, labetalol, captopril.

- **Hypertensive urgency:** Lower to goal within 24 hours with oral medications.
- **Hypertensive emergency:** ↓ mean arterial pressure (MAP) by ~20% within first hour, not exceeding 25% in 24 hours. Do NOT lower too quickly or to normal BP, as autoregulation of BP cannot adjust quickly enough → ischemia (eg, stroke, MI). Classically occurs in a patient with long-standing HTN who stops medications.
- **Medications:** Any IV antihypertensive medication can be acceptable, as the specific drug available is not as important as proper dosing of it to manage BP to goal. Drugs commonly used: β-blockers (labetalol or esmolol), CCBs (clevidipine or nicardipine), D1 agonist (fenoldopam), hydralazine, enalapril, **nitroprusside** (prolonged use → cyanide poisoning → inhibition of electron transport chain [ETC] → severe lactic acidosis).

KEY FACT

Hypertensive emergency is diagnosed based on the presence of hypertension-induced end-organ damage, NOT a specific BP measurement. Generally, however, severe hypertension has an SBP >180 mm Hg or DBP >120 mm Hg present.

KEY FACT

Cyanide poisoning classically presents with hypertensive emergency after nitroprusside therapy with altered mental status + widespread features of tissue hypoxia. Immediately initiate antidote(s):

- Hydroxocobalamin (first-line)
- Sodium thiosulfate (coadminister with hydroxocobalamin)
- Sodium or amyl nitrate

Q

A 20-year-old man presents with an initial BP of 150/85 mm Hg, and repeat measurement yields 147/85 mm Hg. The patient's potassium level is 3.2 mg/dL. What is the next best diagnostic step?

PERICARDIAL DISEASE

The pericardium is a fibroelastic sac made up of visceral and parietal layers separated by a potential space, the pericardial cavity. In healthy individuals, the pericardial cavity contains 30 to 50 mL of an ultrafiltrate of plasma.

Diseases of the pericardium present as acute pericarditis, constrictive pericarditis, pericardial effusion, and cardiac tamponade.

ACUTE PERICARDITIS

Acute pericarditis refers to inflammation of the pericardial sac. It may be either the first manifestation of an underlying systemic disease or represent an isolated process. Etiologies include:

- Idiopathic
- Infectious (most common infection, likely etiology Coxsackie B virus, *Staphylococcus*, *Streptococcus*, tuberculosis [TB])
- Connective tissue disorder (ie, systemic lupus erythematosus [SLE], rheumatoid arthritis, Goodpasture syndrome)
- Post-MI (either within days after MI or as a delayed phenomenon, ie, Dressler syndrome)
- Uremia
- Neoplasms
- Drugs
- Radiation
- Trauma or open heart surgery (Fig. 2.1-24).

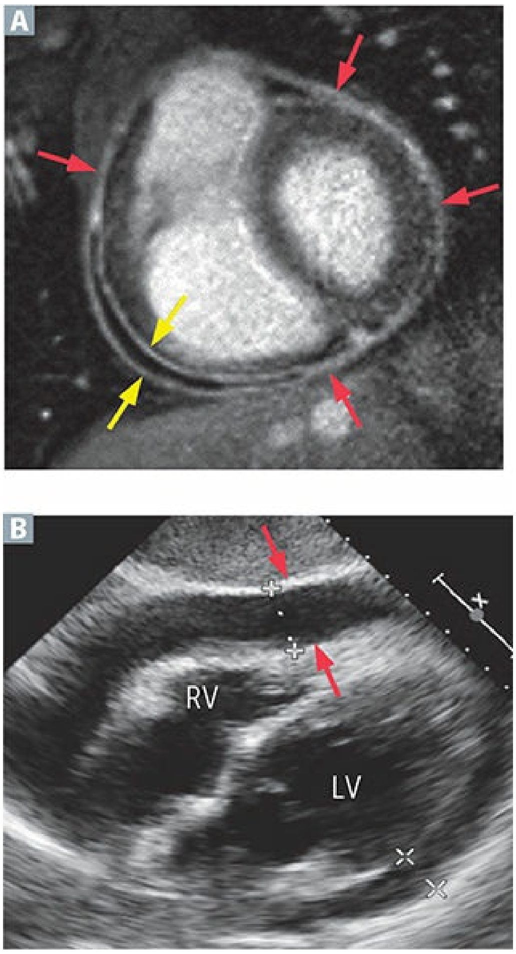


FIGURE 2.1-24. **Radiographic findings in pericarditis. (A)** MRI demonstrates an effusion *(yellow arrows)* within the pericardial sac *(red arrows)*. Pericardial effusion is diagnosed when the pericardial space is >3 to 4 mm in diameter (a normal pericardial space has 30–50 mL of fluid, and this space is ≤2 mm in diameter). **(B)** Echocardiography showing pericardial effusion *(red arrows)*. (Image A adapted with permission from Bogaert J, Francone M. Cardiovascular magnetic resonance in pericardial diseases. *J Cardiovasc Magn Reson.* 2009;11[1]:14. doi:10.1186/1532-429X-11-14. Image B adapted with permission from Yousuf T, Kramer J, Kopiec A, et al. A rare case of cardiac tamponade induced by chronic rheumatoid arthritis. *J Clin Med Res.* 2015;7[9]:720–723. doi:10.14740/jocmr2226w.)

Acute pericarditis can compromise cardiac output via tamponade (extravasation of large amounts of fluid secondary to pericarditis) or constrictive pericarditis (chronic pericarditis).

History/PE

- Presentation: Sharp pleuritic chest pain, dyspnea, cough, and fever.
- Key feature: Chest pain tends to worsen in the supine position and with inspiration. Classically, patient is seen sitting up (pain improves in prone position) and bending forward.
- Exam: May reveal a pericardial friction rub. Elevated JVP, tachycardia, muffled S_1 and S_2, and pulsus paradoxus (↓ in SBP >10 mm Hg on inspiration) can be present with pericardial tamponade. Kussmaul sign can be present with constrictive pericarditis.

Diagnosis

- ECG:
    - Stage 1: Diffuse ST-segment elevation (concave or saddle shaped) and PR-segment

depressions.

  - Stage 2: Normalization of ST segment and PR-segment changes.
  - Stage 3: Development of diffuse T-wave inversions (Fig. 2.1-25). Typically seen after ST segment becomes iso-electric.

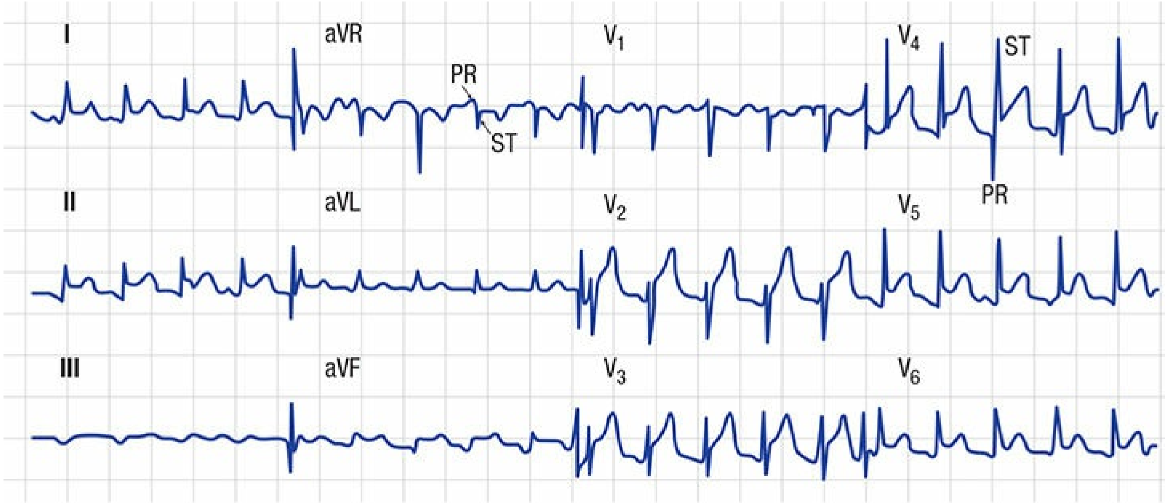


FIGURE 2.1-25. Acute pericarditis. Diffuse ST-segment elevations in multiple leads not consistent with any discrete coronary vascular territory and PR-segment depressions. (Reproduced with permission from USMLE-Rx.com.)

  - Stage 4: Normalization of ECG.
- CXR: Cardiomegaly may indicate a pericardial effusion.

A

A hyperaldosteronism workup with serum aldosterone and renin levels is an appropriate next best diagnostic step.

KEY FACT

Pericardial calcification seen on CXR strongly suggests constrictive pericarditis due to chronic fibrosis and calcification of the pericardium.

- Blood tests: Full blood count (FBC), ESR, urea and electrolytes (U&Es), cardiac enzymes (troponin may be raised), viral serology, and if indicated, autoantibodies, fungal precipitins, and thyroid function tests (TFTs).
- Echo: Pericardial thickening or effusion may be evident.

KEY FACT

ST-segment elevations in pericarditis are differentiated from MI in that they are not localized to one region of the heart; widespread ST-segment elevations are seen.

Treatment

Goal of treatment is pain relief, resolution of inflammation, and prevention of recurrence.

- Activity restriction: Patients should be instructed to restrict strenuous physical activity until symptoms have resolved and biomarkers have normalized.
- NSAIDs + colchicine: For patients with idiopathic or viral pericarditis.
- Glucocorticoids should be used for initial treatment of acute pericarditis only in patients with contraindications to NSAIDs or for specific indications (SLE, renal failure). Avoid corticosteroids within a few days after MI, as they can predispose to ventricular wall rupture.
- For patients in whom etiology for pericarditis is known, specific treatment for the underlying cause is indicated (dialysis in uremia, ASA for post-MI pericarditis, corticosteroids/immunosuppression for SLE-related pericarditis).
- When acute symptoms are resolved, NSAIDs are tapered weekly to reduce recurrence rate, and colchicine is used for a total duration of 3 months.

KEY FACT

Consider uremic pericarditis in a patient with end-stage renal disease and azotemia. It is characterized by prominent fibrin deposition but no epicardial inflammation; thus classical ECG changes (diffuse ST elevation, PR depression) are not seen. Treatment is with hemodialysis.

CONSTRICTIVE PERICARDITIS

Constrictive pericarditis is the result of scarring and consequent loss of the normal elasticity of the pericardial sac. Typically, it is chronic in nature.

History/PE

- Presents with symptoms suggesting fluid overload (edema of lower limbs and ascites) and low cardiac output (fatiguability and dyspnea on exertion).
- Clinical exam: JVD, hepatosplenomegaly, **Kussmaul sign**, and pericardial knock (produced from heart hitting the calcified pericardium in diastole).

Diagnosis

- Echocardiography: Should see septal bounce, respiratory septal shift, pericardial thickening, and a decrease in ventricular filling flow during inspiration.
- CXR: May show calcifications around the cardiac silhouette.
- CT scan shows thickened pericardium.
- ECG may show low-voltage complexes.

Treatment

- Diuretics to control edema and ascites.
- Medical management with NSAIDs and colchicine if features are mild.
- **Pericardial stripping** (ie, surgical removal of the pericardium) is the definitive management. Performed if patient fails medical management or if he or she has severe symptoms.

PERICARDIAL EFFUSION

Pericardial effusion is characterized by an increased amount of fluid in the pericardial cavity. Many patients with pericardial effusion are asymptomatic, and the effusion is detected incidentally. Common causes include idiopathic (most common), malignancy, infections, autoimmune disease, hypothyroidism, ascending aortic dissection, anticoagulants, and medication. In countries where TB is endemic, more than 60% of effusions are due to TB.

History/PE

- Patient may present with signs suggestive of acute pericarditis.
- Important to obtain history for recent illnesses, malignancy, history of TB and vaccination status, autoimmune disorders, history of CKD or renal failure, or history of CHF, hypothyroidism, or liver disease.
- Physical exam may show muffled/distant heart sounds.
- Ewart sign/dullness to percussion at the base of the left inferior scapular border in conjunction with tubular breath sounds and egophony.

Diagnosis

- CXR may show an enlarged, globular, water bottle–shaped heart with a large effusion (Fig. 2.1-26).

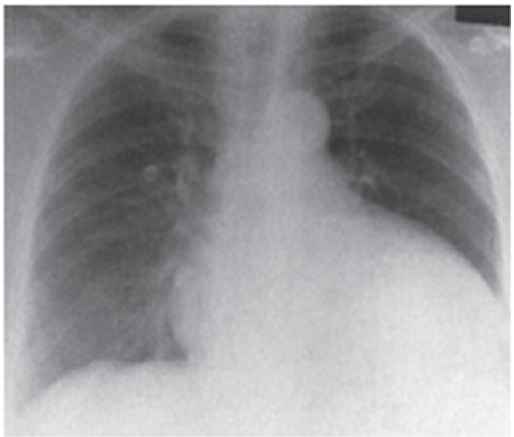


FIGURE 2.1-26. Pericardial effusion. Water bottle–shaped heart seen on CXR with pericardial effusion. (Reproduced with permission from Chen MY et al. *Basic Radiology*, 2nd ed. New York, NY: McGraw-Hill; 2011.)

- Cardiac echo may show increased fluid in pericardial space. On CT imaging, pericardial effusion is diagnosed when the pericardial space is >3 to 4 mm in diameter (a normal pericardial space has 30–50 mL of fluid and is equal to or less than 2 mm in diameter).
- If present on ECG, electrical alternans (due to swinging motion of heart in fluid filled cavity) is diagnostic of a large pericardial effusion (Fig. 2.1-27).

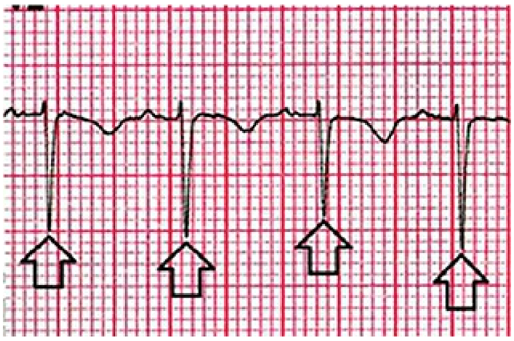


FIGURE 2.1-27. **Electrical alternans, where voltage of QRS changes with each beat. If seen, diagnostic of pericardial effusion.** (Modified with permission from Maharaj SS, Chang SM. Cardiac tamponade as the initial presentation of systemic lupus erythematosus: A case report and review of the literature. *Pediatr Rheumatol Online J.* 2015;13:9. doi: 10.1186/s12969-015-0005-0.)

Treatment

- Treatment focused on the cause of the disease.
- In patients with pericardial effusion of unknown cause and elevated inflammatory markers, empiric treatment for pericarditis is reasonable.
- If cancer or bacterial infection is suspected, pericardiocentesis with or without a pericardial biopsy is recommended.
- If idiopathic effusions are present for more than 3 months, pericardial drainage should be considered, as the likelihood to convert into cardiac tamponade is high in these individuals.
- In patients with symptoms suggestive of cardiac tamponade, immediate pericardial drainage is advised (Cardiac Tamponade section to follow).

CARDIAC TAMPONADE

Excess fluid in the pericardial sac ↑ the intrapericardial pressure, leading to compromised ventricular filling and ↓ cardiac output. The rate of fluid formation is more important than the size of the effusion. Risk factors include pericarditis, malignancy, SLE, TB, and trauma (commonly stab wounds medial to the left nipple).

History/PE

- Presents with fatigue, dyspnea, anxiety, tachycardia, and tachypnea that can rapidly progress to shock and death.
- Exam of a patient with acute tamponade may reveal Beck triad (hypotension, distant or muffled S_1 and S_2 heart sounds, and JVD), a narrow pulse pressure, and pulsus paradoxus.
- **Lung fields are clear on exam** (high yield and frequently tested in CK).

Diagnosis

- Echo is diagnostic and shows right atrial and right ventricular diastolic collapse and echo-free zone around the heart.
- Right heart catheterization will show equalization of all the pressures (RA, RV, pulmonary capillary wedge pressure [PCWP]) in the heart during diastole.

KEY FACT

Beck triad can diagnose acute cardiac tamponade:

- JVD
- Hypotension
- Distant heart sounds

Treatment

- Aggressive volume expansion with IV fluids.
- Urgent pericardiocentesis (aspirate will be nonclotting blood) with a pericardial drain.

Send fluid to lab analysis to determine etiology.

- If significant drainage continues for more than 3 to 4 days or if effusions are recurrent, a pericardial window should be considered.

ENDOCARDITIS

Endocarditis is inflammation of the endocardium, the inner layer of the heart overlying the valves. It has noninfective (NBTE) and infective (bacteria/fungi) causes. Infective endocarditis (IE) is the consequence of bacteremia (dental procedures, injections, surgery) and usually causes tricuspid, mitral, and aortic valve lesions, resulting in regurgitation. Acute IE occurs over hours to days, whereas subacute IE progresses over weeks to months. Causes are discussed in Table 2.1-24.

TABLE 2.1-24. **Etiologies of Endocarditis**

NATIVE VALVE	PROSTHETIC VALVE (HIGHEST RISK)	IVDUS	NON-BACTERIAL THROMBOTIC ENDOCARDITIS (NBTE)
Viridans streptococci (most common, damaged valves) ***Staphylococcus aureus*** (highly virulent, undamaged valves) ***Streptococcus gallolyticus*** (*S bovis* type 1 → colonoscopy) ***Clostridium septicum*** → colonoscopy ***Enterococci* spp.** (older men after GI/GU procedure) **Culture ⊖ organisms,** *Coxiella burnetii* (farm exposure), *Bartonella quintana/henselae* (lice/cat), *Cutibacterium acnes Brucella* (farm), *Mycobacteria* (aerosolized particles), *Tropheryma whipplei* (farm exposure) ***HACEK*** (no longer culture [–] causes of IE with modern culture techniques)	**<60 days surgery:** Early-onset causes *(Staphylococcus epidermidis >> S aureus)* **>60 days surgery:** Late-onset causes *(Streptococci)*	***S aureus*** (most common) *Enterococci* *Streptococci* Fungus *(Candida, Aspergillus* [may see in HIV/AIDS patient]) *Pseudomonas*	**Causes of NBTE:** Immune complexes Hypoxia Hypercoagulability Carcinomatosis **Key terms of NBTE:** Cancer/illnesses → Marantic NBTE Lupus → verrucous or Libman-Sacks NBTE **(both sides of valve[a])** **Key presentation/finding:** Asymptomatic, found on autopsy. Symptomatic → **sterile** lesions of thrombus + immune complexes on left-sided valves (most common) **embolize** → systemic circulation. **Treatment:** Anticoagulation

[a] NBTE and infective causes of endocarditis usually infect and cause lesions on one side of the valve.

Select organisms from Table 2.1-24:

- ***Staphylococcus aureus:*** Gram/catalase/coagulase ⊕ cocci → Use of IV drugs may result in cocci from skin being introduced into veins → high virulence → *attacks normal* right-sided heart valves (tricuspid valve → tricuspid regurgitation). Most common cause of acute IE in all patients (fatal without treatment in 6 weeks). Infects any heart valve (Fig. 2.1-28A).

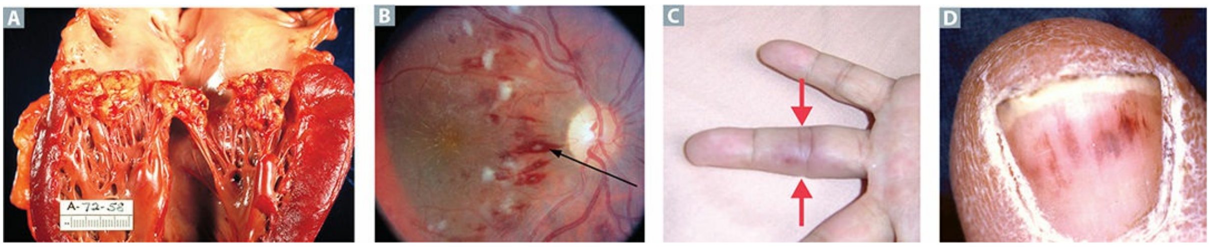


FIGURE 2.1-28. **Features of infective endocarditis. (A)** Large vegetations due to *Haemophilus parainfluenzae;* **(B)** Roth spots on the retina; **(C)** Osler nodes; **(D)** splinter hemorrhages. (Image A adapted with permission from The US Department of Health and Human Services and Dr. Edwin P. Ewing, Jr. Image C Yang ML, Chen YH, Lin WR, et al. Case report: infective endocarditis caused by *Brevundimonas vesicularis. BMC*

Infect Dis. 2006;6:179. DOI: 10.1186/1471-2334-6-179. Images B and D reproduced with permission from USMLE-Rx.com.)

- ***Staphylococcus epidermidis:*** Gram/catalase ⊕ and coagulase ⊖ cocci of skin flora. Low virulence → usually need prosthetic heart valves to cause IE.
- ***Viridans streptococci (S mitis, S mutans, S sanguinis):*** Gram ⊕ and catalase ⊖ cocci of oral flora. Most common cause of subacute endocarditis. Dental procedure → bacteremia → low virulence → *Viridans* produce dextrans → dextrans adhere to fibrin on *damaged valve* → IE.
- ***Streptococcus gallolyticus (S bovis type 1) and Clostridium septicum*** are gram ⊕ cocci and rods, respectively, normally found in the GI tract. If either one causes IE, **a colonoscopy** is indicated because both are associated with colonic pathology, especially **colon cancer.**
- ***Enterococci:*** Gram ⊕ cocci normally found in the GI tract. After **GI or genitourinary (GU) procedures** (abdominal surgery, urinary catheter, transurethral resection of prostate for benign prostatic hypertrophy [BPH]) → subacute endocarditis in **older men.**
- ***HACEK: H****aemophilus* species (subsequently called *Aggregatibacter aphrophilus* + *Aggregatibacter paraphrophilus*); ***A****ctinobacillus actinomycetemcomitans* (subsequently called *Aggregatibacter actinomycetemcomitans*); ***C****ardiobacterium hominis;* ***E****ikenella corrodens; and* ***K****ingella kingae.* Normal flora of oropharyngeal region that typically cause subacute IE associated with poor dental hygiene/procedures. **No longer considered important causes of culture ⊖ IE with modern culture techniques.**
- ***Candida + Aspergillus fumigatus:*** Most common causes of fungal endocarditis typically in immunocompromised patients (HIV/AIDS, transplant), IV drug use (IVDUs), long-term IV catheter use.
- **Culture negative IE:** Most common manifestation of chronic Q fever *(Coxiella burnetii). Bartonella quintana* Gram ⊖ rod → lice spread → individuals with poor hygeine.

History/PE

- **IE** should be suspected in any patient with unexplained fever(s) ± bacteremia and a new regurgitant heart murmur of the tricuspid, mitral, or aortic valve. Fulminant HF due to severe regurgitant lesions may also occur.
- **Septic emboli:** Coronary artery (MI), brain (stroke), spinal cord (paralysis), eye (blindness), extremities (septic arthritis), splenic/renal infarctions, PE (from tricuspid lesions), mycotic aneurysm, abscesses, Janeway lesions (painless erythematous microabscesses on palms/soles).
- **Immune phenomena:** Eyes (Roth spots = oval red retinal lesions with clear/pale center; see Fig. 2.1-28B), glomerulus (signs/symptoms of glomerulonephritis), Osler nodes (painful/raised lesions on digits/feet; "Ouchler nodes," see Fig. 2.1-28C), splinter hemorrhages (vasculitis underneath fingernails that follows direction of growth, see Fig. 2.1-28D), rheumatoid factor.
- **Paravalvular abscess:** Persistent fever + bacteremia despite treatment → paravalvular abscess formation. Notably, paravalvular abscess of aortic valve → new-onset AV block on ECG.

MNEMONIC

Presentation of Infective Endocarditis—

FROM JANE with ♥

Fever
Roth spots
Osler nodes (painful, “Ouchler nodes”)
Murmur
Janeway lesions (“Mary Jane is painless”)
Anemia of chronic disease
Nail hemorrhage
Emboli

Diagnosis

- CBC with leukocytosis and left shift,↑ ESR and C-reactive protein (CRP) may be seen.
- Duke clinical criteria (see mnemonic and Table 2.1-25). Two major, one major + three minor, or five minor criteria must be present to diagnose IE.

TABLE 2.1-25. **Duke Clinical Criteria for the Diagnosis of Infective Endocarditis**

CRITERIA	COMPONENTS	MNEMONIC
Major	1. **B**acteremia (one of the following): two separate ⊕ blood cultures of typical IE organisms (*Staphylococcus, Streptococcus,* enterococci, HACEK) or persistently ⊕ blood cultures (at least two samples drawn >12 hours apart for typical IE organisms or three or majority of >4 separate blood cultures for typical skin contaminant organisms with the first and last drawn at least 1 hour apart) or single ⊕ blood culture or phase IgG antibody titer for *Coxiella burnetii.* 2. **E**ndocardial involvement (one of the following): echocardiogram evidence of vegetation, abscess, valve perforation, or prosthetic dehiscence or *new* valvular regurgitation murmur	**BE**
Minor	1. **F**ever ≥38°C (100.4°F) 2. **I**mmune phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor 3. **V**ascular phenomena: septic arterial/pulmonary emboli, mycotic aneurysm, intracranial/conjunctival hemorrhages, Janeway lesions 4. **O**rganism culture not meeting major criteria or serologic evidence of active infection with IE organism 5. **R**isk factors: abnormal risk of bacteremia (IVDUs) or abnormal heart (prosthetic valve or lesion with significant regurgitation)	**fivor**

- **Best initial test:** Blood culture (95%–99% sensitive).
- **Best imaging test:** TEE (95% sensitive/specific) > TTE (60% sensitive, 95%–100% specific) in diagnosing endocarditis. Most patients should first get a TTE as initial screening test.
- **ECG** not routinely used. If treatment failures, aortic paravalvular abscess → new AV block.

MNEMONIC

Duke Criteria Mnemonic: “BE Duke fivor”

Step 1:

- Capital letters = Major Criteria.
- Lowercase letters = minor criteria.
- The number/type of letters in each word then represents a diagnostic category:
- Two Major Criteria (**BE**).

- One Major + three minor (**Duke**) or five minor criteria (**fivor**)

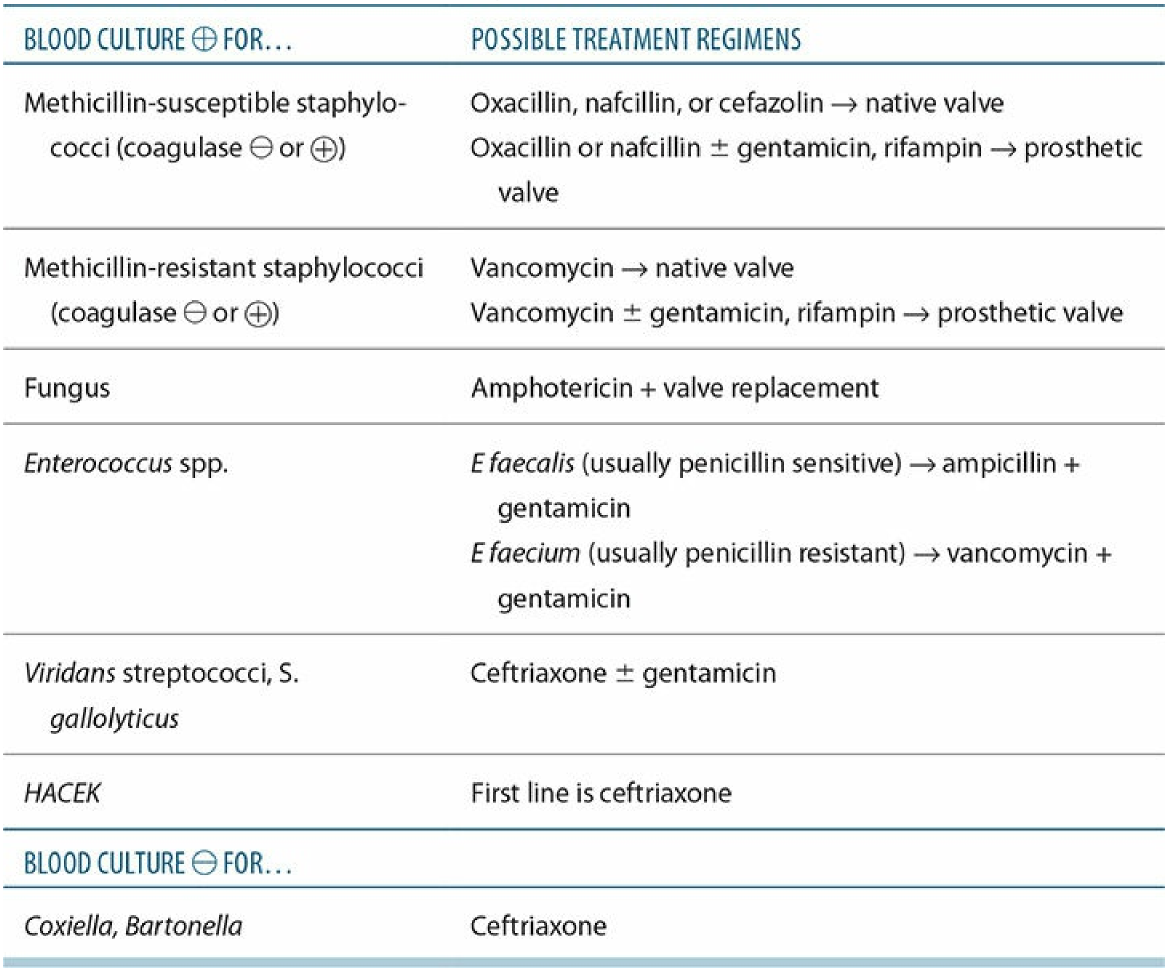
Step 2

- **BE:** (**B**acteremia [blood cultures] + **E**ndocardial involvement [echo or murmur]) = Major Criteria
- **Duke** (diagnostic category, name of criteria)
- **fivor:** (**f**ever, **i**mmune phenomena, **v**ascular phenomena, **o**rganism cultures not meeting major criteria, **r**isk factors) = minor criteria

Treatment

- **General guidelines:** At least two, preferably three, sets of blood cultures should be drawn prior to initiating antibiotics, generally even in acutely ill patients. If empiric antibiotics are given for native or prosthetic valve endocarditis, the **best initial treatment is vancomycin ± gentamicin** or another antibiotic. Blood culture results are used to tailor therapy. Antibiotics are delivered parenterally for 4 to 6 weeks for left-sided lesions and 2 weeks for right-sided lesions, and are targeted toward the specific microorganism (Table 2.1-26).

TABLE 2.1-26. **Targeted Treatment Regimens for Infective Endocarditis**



BLOOD CULTURE ⊕ FOR…	POSSIBLE TREATMENT REGIMENS
Methicillin-susceptible staphylococci (coagulase ⊖ or ⊕)	Oxacillin, nafcillin, or cefazolin → native valve Oxacillin or nafcillin ± gentamicin, rifampin → prosthetic valve
Methicillin-resistant staphylococci (coagulase ⊖ or ⊕)	Vancomycin → native valve Vancomycin ± gentamicin, rifampin → prosthetic valve
Fungus	Amphotericin + valve replacement
Enterococcus spp.	*E faecalis* (usually penicillin sensitive) → ampicillin + gentamicin *E faecium* (usually penicillin resistant) → vancomycin + gentamicin
Viridans streptococci, S. *gallolyticus*	Ceftriaxone ± gentamicin
HACEK	First line is ceftriaxone
BLOOD CULTURE ⊖ FOR…	
Coxiella, Bartonella	Ceftriaxone

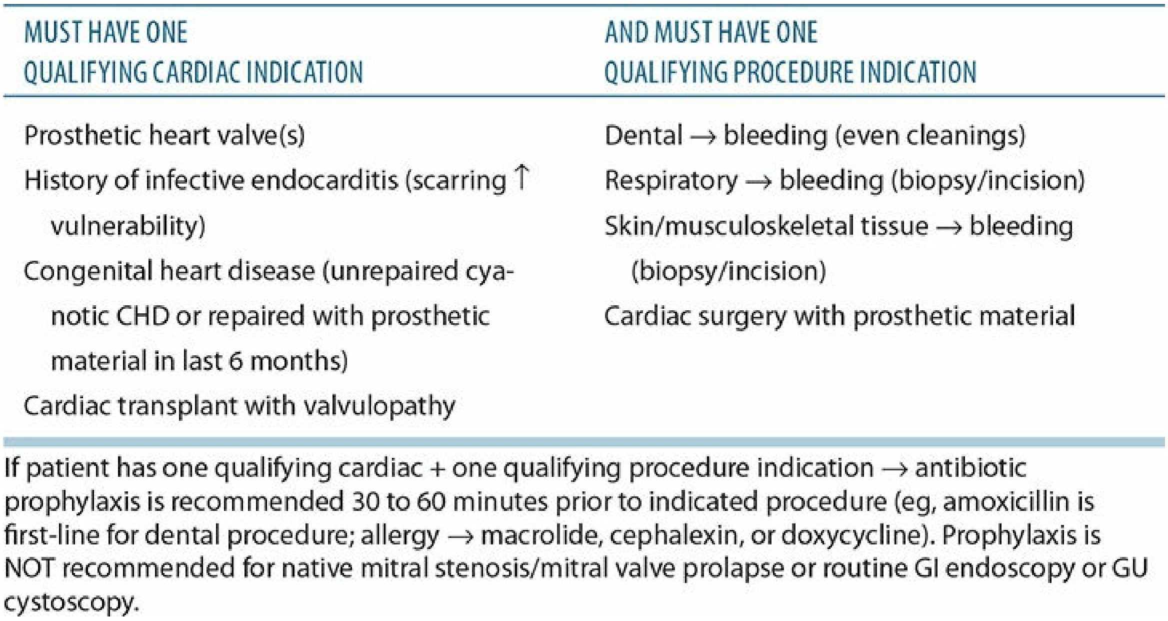
- **Surgical considerations:** Early surgical consultation + intervention is considered with
  - Valvular damage → acute HF
  - Fungal IE
  - Left-sided IE with highly resistant microbes (eg, methicillin-resistant *S aureus*

[MRSA])
- Persistent fever or bacteremia 5 to 7 days post-antibiotic treatment
- Prosthetic valves
- Antibiotics cannot penetrate large vegetations: Vegetation >15 mm or vegetation >10 mm + systemic emboli
- Perivalvular extension (eg, paravalvular abscess: aortic paravalvular abscess → new-onset AV block), pseudoaneurysm, or fistula formation

Prophylaxis

Prophylactic antibiotics may be indicated to prevent IE in certain patients at high risk of poor outcomes. These are discussed in Table 2.1-27.

TABLE 2.1-27. **Indications for Endocarditis Antibiotic Prophylaxis**



MUST HAVE ONE QUALIFYING CARDIAC INDICATION	AND MUST HAVE ONE QUALIFYING PROCEDURE INDICATION
Prosthetic heart valve(s)	Dental → bleeding (even cleanings)
History of infective endocarditis (scarring ↑ vulnerability)	Respiratory → bleeding (biopsy/incision)
Congenital heart disease (unrepaired cyanotic CHD or repaired with prosthetic material in last 6 months)	Skin/musculoskeletal tissue → bleeding (biopsy/incision)
Cardiac transplant with valvulopathy	Cardiac surgery with prosthetic material

If patient has one qualifying cardiac + one qualifying procedure indication → antibiotic prophylaxis is recommended 30 to 60 minutes prior to indicated procedure (eg, amoxicillin is first-line for dental procedure; allergy → macrolide, cephalexin, or doxycycline). Prophylaxis is NOT recommended for native mitral stenosis/mitral valve prolapse or routine GI endoscopy or GU cystoscopy.

VALVULAR HEART DISEASE

Subtypes of valvular heart disease appear in Table 2.1-28 along with their specific etiologies, presentations, diagnoses, and treatments. Overarching high-yield concepts for all valvular diseases are briefly presented.

TABLE 2.1-28. **Types, Etiologies, Clinical Features, and Diagnosis/Treatment of Valvular Lesions**

TYPE	ETIOLOGIES	CLINICAL FEATURES	DIAGNOSIS/TREATMENT
Aortic Stenosis (AS)	**Senile AS** Most common Dystrophic calcification of a tricuspid valve Elderly >60 years of age **Bicuspid AS** Congenital, Turner disease Dystrophic calcification of a bicuspid valve <60 years of age **Rheumatic heart disease (RHD) AS** Distinguished by commissure fusion	**Signs/Symptoms** Asymptomatic: Years despite severe stenosis Symptomatic: **A**ngina, **S**yncope, **C**HF (**ASC**), in order of worsening prognosis without treatment Murmur: Harsh systolic crescendo-decrescendo murmur, heard best at the second right intercostal space, radiates to carotids, paradoxical splitting due to delayed LV outflow Increase murmur = Increase venous return and decrease afterload Severe AS: Soft, single S2 as cusp movement becomes more restricted; pulsus parvus et tardus (weak/delayed carotid upstroke); late-peaking murmur; LVH develops → LV dilates once cannot compensate → heart failure without treatment	**Diagnosis** Severity categorized based on pressure gradient across aortic valve or valve area into mild (15–25 mm Hg, >1.5 cm^2), moderate (25–40 mm Hg, 1.0–1.5 cm^2), severe (>40 mm Hg, 0.7–1.0 cm^2) or critical (<0.7 cm^2) TTE is best initial test Severity of stenosis can also be assessed from TTE **Treatment** Based on severity Asymptomatic: No treatment Severe stenosis with symptoms **or** LVEF <50% **or** other planned cardiac surgery: surgical valve replacement or transcatheter aortic valve replacement (TAVR), which is the superior option in appropriate patients
Aortic Regurgitation (AR) or Aortic Insufficiency	**Causes of AR:** **Root Dilation** Inflammation (syphilis, ankylosing spondylitis), trauma, aortic dissection, MI, HTN-induced/Marfan-related aortic aneurysm **Valve Disease** RHD, bicuspid valve (AS > AR), connective tissue disorders, endocarditis	**Signs/Symptoms** Acute (aortic dissection, endocarditis) → shock Chronic: Angina, palpitations, heart failure Murmur: Early blowing decrescendo diastolic murmur, heard best at third left intercostal space May also hear Austin Flint murmur at apex Increase murmur = Increase venous return and increase afterload **Wide pulse pressure** is central to AR: Blood leaks into LV in diastole, which ↓ DBP and ↑ preload/SV which ↑ SBP; hyperdynamic circulation can lead to bounding pulses, nail bed pulsations, head/uvula bobbing with heartbeat, and femoral bruit; volume overload leads to eccentric hypertrophy of LV and displacement of PMI down and to the left	**Diagnosis** TTE is best initial test **Treatment** Acute AR: Emergent valve surgery Chronic AR: Use of vasodilators to decrease afterload, but they don't delay progression Serial TTEs are done to monitor LV dilation and need for valve replacement, the definitive treatment
Mitral Stenosis (MS)	**Chronic Rheumatic Heart Disease** Untreated streptococcal infections lead to bouts of acute rheumatic fever → scarring/fibrous and commissure fusion of mitral valve Rare in United States Young adult immigrant is classic	**Signs/Symptoms** Patient may not recall history of rheumatic fever ↑ left atrial pressure → pulmonary congestion (dyspnea, orthopnea, PND, hemoptysis, **pulmonary HTN**/RV failure); ↑ left atrial size (**A-fib/thrombus/stroke;** laryngeal nerve/esophagus compression = dysphagia/hoarseness) Murmur: Opening snap (think: steno-snap) with mid-diastolic rumbling at apex Loud S1 with valve closer; the closer in time the opening snap is to S2, the worse stenosis is; loud S2 with pulmonary HTN Increase murmur = increase venous return and decrease afterload	**Diagnosis** TTE is best initial test **Treatment** Diuretics cautiously treat congestion β-blockers, CCBs, digoxin for rate control to ↑ filling time; tachycardia is poorly tolerated Warfarin first-line for valvular A-fib Surgical valve repair/replacement or catheter-based balloon valvuloplasty only for severe + symptomatic MS due to RHD, as it can break up fibrous tissue

TYPE	ETIOLOGIES	CLINICAL FEATURES	DIAGNOSIS/TREATMENT
Mitral Regurgitation (MR) Mitral valve prolapse (MVP)	**Primary MR** MVP (myxomatous): Sporadic, familial, connective tissue disease (EDS/Marfan) **Acute secondary MR** Posteromedial papillary muscle rupture due to posterior descending artery occlusion or ischemic dysfunction with MI, endocarditis **Chronic secondary MR** Rheumatic fever, **"functional MR"** LV dilates, ↑ annulus, normal cusps ≠ close	**Signs/Symptoms** **Primary MR:** Most patients are asymptomatic, may be related to anxiety, murmur detected Murmur: Leaflets billow above annulus → midsystolic nonejection click + MR murmur **Increase murmur = reduce LV size** by decreasing venous return (stand/Valsalva); think: Billowing leaflets are like a parachute—small parachute is bad, small LV size is bad **Acute secondary MR:** Abrupt ↑ left atrial pressure → flash pulmonary congestion, hypotension, shock **Chronic secondary MR:** Asymptomatic to heart failure Murmur: Holosystolic at apex, radiates to axilla Increase murmur = Increase venous return and increase afterload	**Diagnosis** TTE for first-/second-degree MR **Treatment** First-degree MR: Reassurance Acute second-degree MR: Emergent valve surgery Chronic second-degree MR: Use of vasodilators to decrease afterload, don't delay progression; manage heart failure/A-fib **Functional MR treat with diuretic to ↓ LV size;** surgery if severe: Prefer clipping valve > replacing
Tricuspid Regurgitation (TR)	**Tricuspid endocarditis (IV drug use)** **Ebstein anomaly** (congenital downward displacement of tricuspid valve → RV); carcinoid syndrome (see later), lupus, myxomatous degeneration **Normal:** Up to 70% of adults have physiologic TR; majority are asymptomatic **RV dilation:** LV failure (most common), RV MI, inferior wall MI, pulmonary HTN → cor pulmonale.	**Signs/Symptoms** Majority asymptomatic → symptoms manifest with pulmonary HTN→ right HF and may include ascites, pulsatile/enlarged liver, edema, prominent V waves + rapid y descent in jugular venous pulse, JVD; right atrial dilatation → AF Murmur: Sound of TR murmur = second-degree MR murmur (holosystolic) but is at lower-left sternal border Increase murmur = ↑ venous return via inhalation (like sipping a straw) + leg raise	**Diagnosis** TTE is best initial test; can assess pulmonary pressures via TR velocity **Treatment** Treat underlying cause Diuretics for congestion Surgery for severe + symptomatic TR without pulmonary HTN

Right-sided valve disease: Murmur-like left-sided counterpart with different listening area. Tricuspid/pulmonic stenosis/regurgitation is caused by carcinoid heart disease (tumor releases serotonin → neutralized in lungs = only right-sided valves coated/fibrosed). **TR:** classically endocarditis in IVDU, RV enlargement. **PR** classically in TOF patient years after repair.

- **Identification:** Murmur descriptions are usually the most specific identifiers in questions. Right-sided murmurs increase in intensity with inhalation (like sipping a straw, this increases venous return), whereas left-sided murmurs decrease with inhalation. Exhalation is the exact opposite.
- **Rheumatic heart disease** can cause any valvular disease. Mitral stenosis is most common.
- **Best initial test: Echocardiogram.** TTE is less invasive; TEE is more sensitive/specific.
- **Most accurate test: Cardiac catheterization,** which measures valvular diameters and pressure gradients.
- **Not ECG/x-ray:** Often listed as answer distractions. Both can indicate chamber enlargement.

Broad treatment guidelines:

- **Endocarditis prophylaxis** is only for replaced valves or valves with previous endocarditis.
- **Diuretics** are helpful for fluid overload that can occur in all forms of valvular heart

diseases.
- **Surgery** is indicated only for symptomatic + severe valvular disease.
- **Severe stenotic lesions** are treated with surgery to restore functional anatomy.
- **Severe regurgitant lesions** can initially be treated with vasodilators to decrease afterload and encourage forward blood flow. Surgery is done prior to significant dilatation of the heart.

KEY FACT

Mitral regurgitation classically occurs secondary to posteromedial papillary muscle rupture 2 to 7 days after a posterior descending coronary artery MI due to its singular blood supply. Conversely, anterolateral papillary muscle rupture is 6 to12 times less likely due to its dual blood supply from the left anterior descending + left circumflex arteries.

KEY FACT

Many cardiovascular conditions have an increased risk during pregnancy. For example, pregnancy is not advised with severe obstructive valvular lesions (mitral stenosis, aortic stenosis), symptomatic HF with EF <30%, unstable/dilated aorta (eg, Marfan syndrome), and pulmonary HTN.

VASCULAR DISEASES

AORTIC ANEURYSM

Greater than 50% dilation of all three layers of the aortic wall. Aortic aneurysms are most commonly associated with atherosclerosis. Most are abdominal, and >90% originate below the renal arteries.

- **Etiologies:** Degeneration (atherosclerosis, fibromuscular dysplasia), infection (syphilis), trauma, inflammation (Takayasu), connective tissue diseases (Marfans, Ehlers-Danlos syndrome), and congenital (Turner syndrome, tuberous sclerosis)
  - Ascending aortic aneurysm—think cystic medial necrosis or connective tissue disease
  - Descending aortic aneurysm—think atherosclerosis
- **Complications:** Rupture, thrombosis, embolism, fistulae, pressure on surrounding structures

History/PE

- Usually asymptomatic and discovered incidentally on exam or radiologic study. It may cause mild abdominal or back pain. Less frequently, those with symptomatic but unruptured aneurysms may present with signs of limb ischemia (acute or chronic) or systemic symptoms (fever, malaise).
- Exam can demonstrate a pulsatile abdominal mass or abdominal bruits.
- Risk factors include HTN, high cholesterol, other vascular disease, a ⊕ family history, smoking (strongest predictor of rupture), gender (males > females), and age.
- Ruptured aneurysm leads to hypotension and severe, tearing abdominal pain that radiates to the back, iliac fossae, or groin and syncope.

KEY FACT

AAA is generally defined as abdominal aortic dilation in adults >3.0 cm.

Diagnosis

- **Screening:** All men 65 to 75 years of age with a history of smoking are recommended for a one-time screening by ultrasound for AAA (Fig. 2.1-29). Figure 2.1-30 suggests an algorithm for the diagnosis and initial management of AAA.

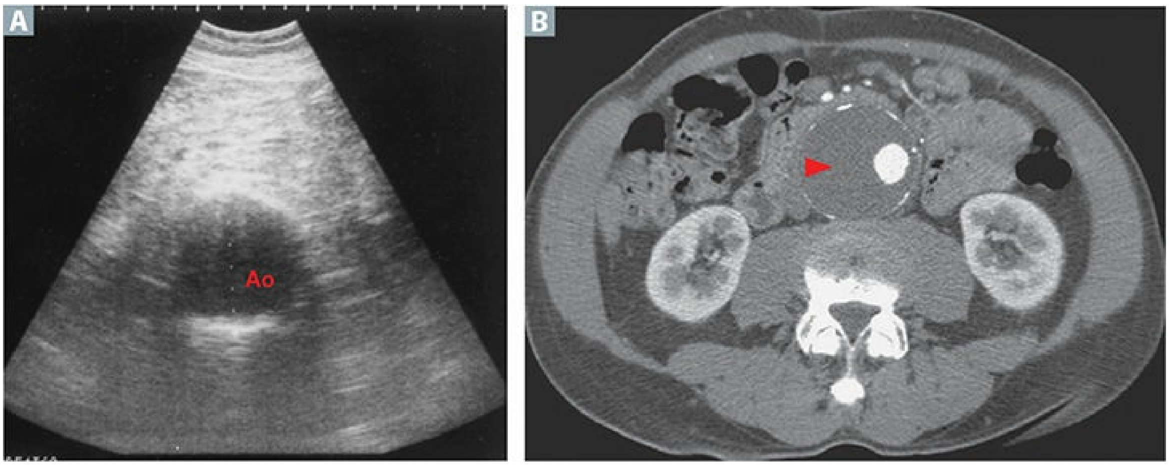


FIGURE 2.1-29. **Abdominal aortic aneurysm. (A)** Ultrasound image of an AAA (*Ao*, Aorta). **(B)** Transaxial image from a contrast-enhanced CT showing an aneurysm with extensive mural thrombus *(arrowhead)*. (A reproduced with permission from Tintinalli JE et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide* 6th ed. New York, NY: McGraw-Hill; 2004. B reproduced with permission from Doherty GM. *Current Diagnosis & Treatment: Surgery* 13th ed. New York, NY: McGraw-Hill; 2010.)

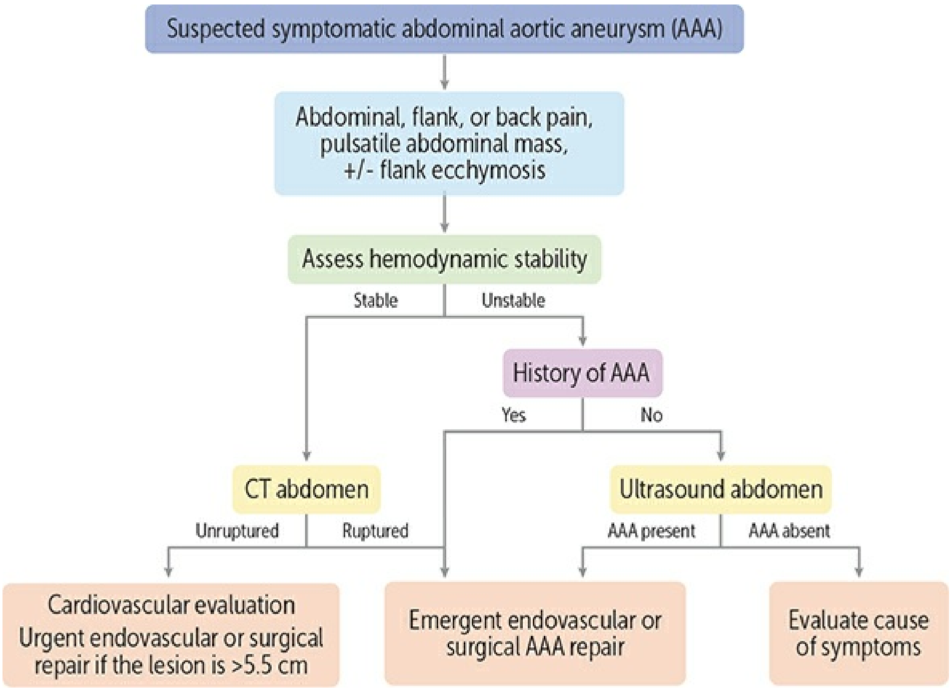

Suspected symptomatic abdominal aortic aneurysm (AAA)
Abdominal, flank, or back pain, pulsatile abdominal mass, +/- flank ecchymosis
Assess hemodynamic stability
Stable
Unstable
History of AAA
Yes
No
CT abdomen
Ultrasound abdomen
Unruptured
Ruptured
AAA present
AAA absent
Cardiovascular evaluation Urgent endovascular or surgical repair if the lesion is >5.5 cm
Emergent endovascular or surgical AAA repair
Evaluate cause of symptoms

FIGURE 2.1-30. **Diagnosis of suspected abdominal aortic aneurysm (AAA).** (Reproduced with permission from USMLE-Rx.com.)

- Abdominal ultrasound is used for diagnosis or to follow the course of an aneurysm over time.

Q

A 70-year-old man with HTN presents for a routine appointment. He quit smoking 20 years ago but has a 20-pack-year history. What screening, if any, is indicated?

- CT with contrast or magnetic resonance angiography (MRA) may be useful to determine the precise anatomy.

KEY FACT

Size of AAA determines treatment:

- <5 cm → monitoring
- >5 cm → surgical correction

Treatment

- In asymptomatic patients, monitoring is appropriate for lesions
- Surgical or endovascular correction is indicated if the lesion is ≥5.5 cm (abdominal), >6 cm (thoracic), or smaller but rapidly enlarging (watch for bowel ischemia and infarction).
- Emergent surgery for symptomatic or ruptured aneurysms.

KEY FACT

Rapidly expanding aortic aneurysms are defined as >5 mm increase in size in 6 months or >10 mm increase in size in 12 months.

AORTIC DISSECTION

A transverse tear in the intima of a vessel that results in blood entering the media, creating a false lumen and leading to a hematoma that propagates longitudinally. Most commonly secondary to HTN, but also due to blunt chest trauma. The most common sites of origin are above the aortic valve and distal to the left subclavian artery. Most often occurs at 40 to 60 years of age, with a greater frequency in males than in females.

KEY FACT

Aortic aneurysm is most often associated with atherosclerosis, whereas aortic dissection is commonly linked to HTN.

History/PE

- **History:** HTN, Marfan syndrome, mitral valve prolapse, trauma
- **Presentation:** Sudden tearing/ripping pain in the anterior chest (ascending) with or without radiation to the back (descending), typically between the scapulae
- **PE:**

- Patients are typically hypertensive. If hypotensive, consider pericardial tamponade, hypovolemia from blood loss, or other cardiopulmonary etiologies.

> A
>
> The United States Preventive Services Task Force (USPSTF) guidelines recommend one-time screening for AAA by ultrasound in men 65 to 75 years of age who have ever smoked.

- Asymmetric pulses and BP measurements or acute limb ischemia.
- A murmur of aortic regurgitation may be heard if the aortic valve is involved with a proximal dissection.
- Neurologic deficits, such as paraplegia, may be seen if the aortic arch or spinal arteries are involved.
- Anuria may be seen if renal arteries are involved.
- Signs of pericarditis or pericardial tamponade may be seen.

Diagnosis

- Aortic dissection suspected based on history and physical exam findings.
- **Best initial test for hemodynamically stable patients:** CT angiography. MRA can be used if contrast CT is contraindicated.
- TEE. Visualization of an intimal flap as well as a false lumen is diagnostic. It may also be used to visualize details of the proximal aorta and coronary vessels and can also evaluate for pericardial effusion.
- The Stanford system classifies any dissection proximal to the left subclavian artery as type A and all others as type B (Fig. 2.1-31).

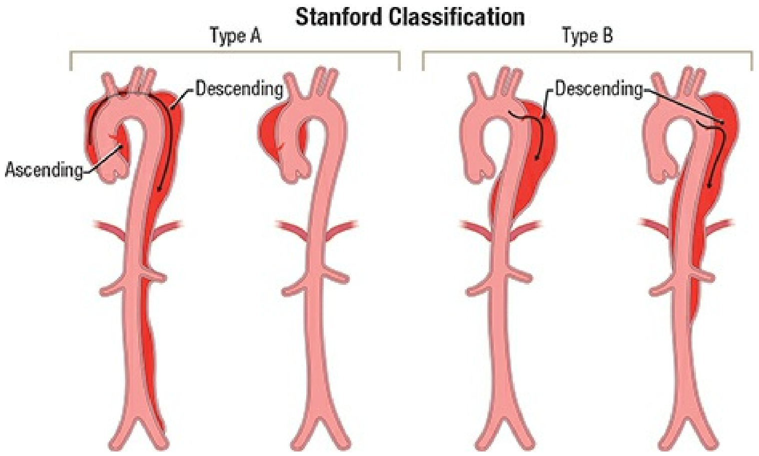


FIGURE 2.1-31. **Stanford classification of aortic dissection.** Type A involves the ascending aorta and may progress to involve the arch and thoracoabdominal aorta. Type B involves the descending thoracic or thoracoabdominal aorta distal to the left subclavian artery without involvement of the ascending aorta. (Reproduced with permission from USMLE-Rx.com.)

- See diagnostic algorithm in Fig. 2.1-32.

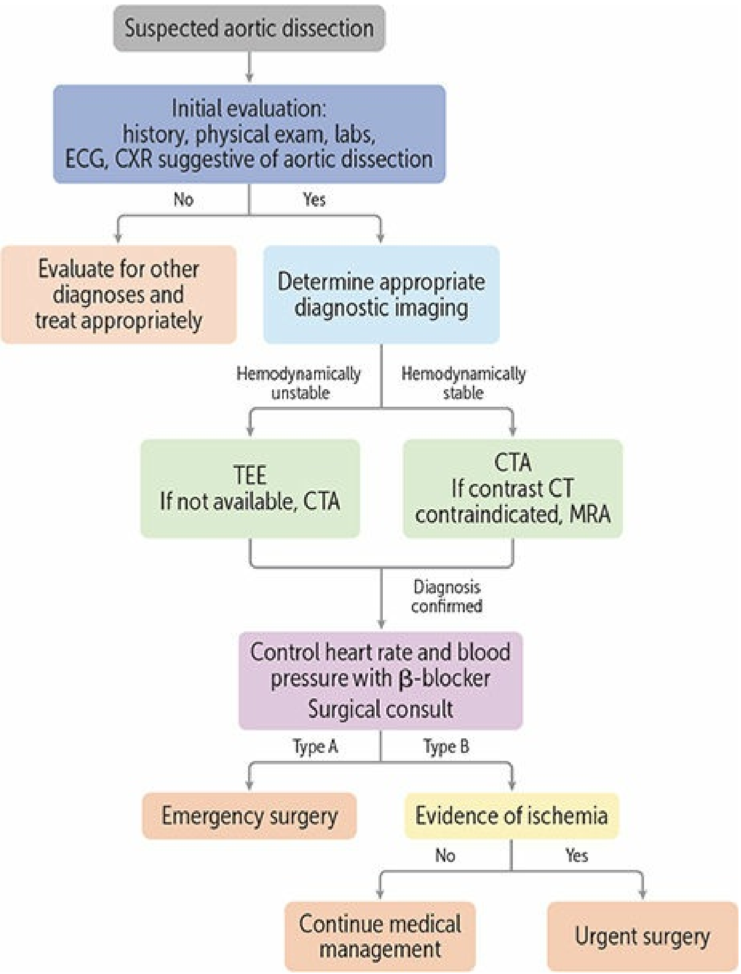

Suspected aortic dissection
Initial evaluation: history, physical exam, labs, ECG, CXR suggestive of aortic dissection
No
Yes
Evaluate for other diagnoses and treat appropriately
Determine appropriate diagnostic imaging
Hemodynamically unstable
Hemodynamically stable
TEE If not available, CTA
CTA If contrast CT contraindicated, MRA
Diagnosis confirmed
Control heart rate and blood pressure with β-blocker Surgical consult
Type A
Type B
Emergency surgery
Evidence of ischemia
No
Yes
Continue medical management
Urgent surgery

FIGURE 2.1-32. **Diagnosis of suspected aortic dissection.** (Reproduced with permission from USMLE-Rx.com.)

- Type A (~70%) is the most common and involves the ascending aorta, irrespective of the site of the tear. Type B does not involve the ascending aorta.

KEY FACT

Ascending aortic dissections are surgical emergencies; descending dissections are still emergencies but can often be treated medically.

Treatment

- **BP control:** Important to monitor and medically manage BP and heart rate as necessary. Avoid thrombolytics. Begin IV β-blockers (eg, IV labetalol) before starting vasodilators (nitroprusside) to prevent reflex tachycardia. BP goals in the management of aortic dissection aim to decrease shear stress on the dissection, but maintain adequate organ perfusion with systolic blood pressure of 100 to 120 mm Hg. Heart rate goal is <60 bpm.
- All patients with type A thoracic dissection (ascending dissections) should have surgery.
- Patients with type B thoracic dissection (descending dissections) may be managed medically with BP and heart rate control; surgery is reserved if there is a leakage, rupture, or compromised organs.

DEEP VENOUS THROMBOSIS

Clot formation in the large veins of the extremities or pelvis. The classic Virchow triad of risk factors includes venous stasis (eg, from long-haul flights, prolonged bed rest, obesity, immobility, or incompetent venous valves in the lower extremities), endothelial trauma (eg, surgery, injury to the lower extremities, IV catheters, trauma), and hypercoagulable states (eg, thrombophilia, malignancy, pregnancy, OCP use, hyperhomocysteinemia). A common scoring system for determining the likelihood of a deep venous thrombosis (DVT)—the Wells' DVT Criteria—guides management of a patient with suspected DVT (Table 2.1-28).

TABLE 2.1-28. Wells' DVT Criteria[a]

CRITERIA	SCORE
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swelling	1
Calf swelling at least 3 cm larger than that on the asymptomatic leg (measured 10 cm below the tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2

[a] High probability of DVT if score is 3 or more, moderate if score is 1 or 2, and low if score is 0 or less.

KEY FACT

Virchow triad: (1) venous stasis, (2) trauma (endothelial damage), (3) hypercoagulability

History/PE

- Presents with unilateral lower extremity pain and swelling. Calf warmth, tenderness, and erythema may be present.
- Homans sign is calf tenderness with passive foot dorsiflexion (poor sensitivity and specificity for DVT).
- Use pretest clinical probability scoring for DVT, the Wells' score.
- May see phlegmasia alba dolens or phlegmasia cerulea dolens (see Fig. 2.1.33) in more severe cases.

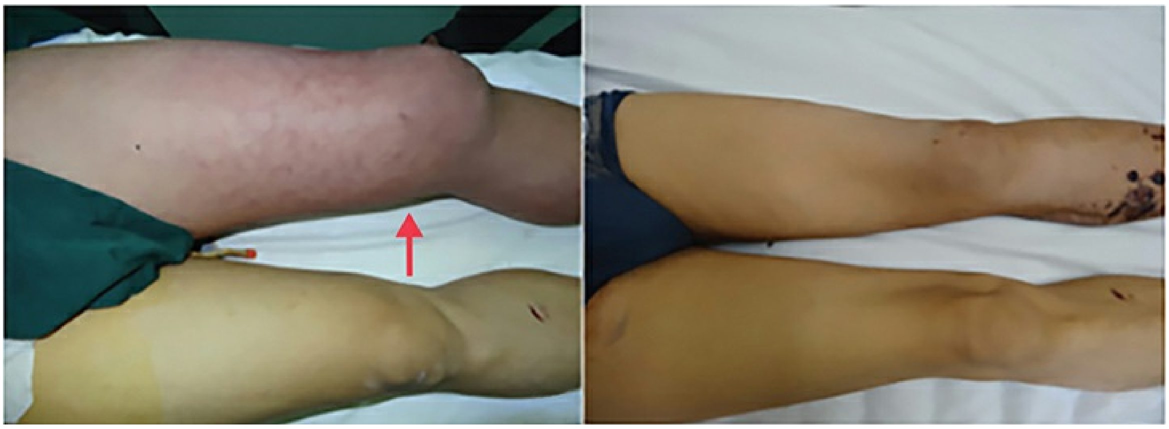


FIGURE 2.1-33. **Phlegmasia cerulea dolens.** (Adapted with permission from Hu H, Cai Y, Wang C, et al. Successful treatment of posttraumatic phlegmasia cerulea dolens by reconstructing the external iliac vein: a case report. *J Med Case Rep.* 2014;8:149 doi:10.1186/1752-1947-8-149)

- Important differential diagnosis includes Baker cyst, muscle strain/tear/twisting injury to leg, cellulitis, edema secondary to infection, and varicose veins.

KEY FACT

Phlegmasia alba dolens (literally, “edema, pain, and white, blanching skin”) is a PE finding sometimes seen in acute DVT.

Phlegmasia cerulea dolens (“edema, pain, and blue skin”) is a more severe form of phlegmasia alba dolens, where the skin turns blue as the DVT progressively worsens (Fig. 2.1-33).

Diagnosis

Moderate- or high-sensitivity D-dimer and lower extremity ultrasound may be ordered based on pretest probability of DVT (see Fig. 2.1-34 for management recommendations).

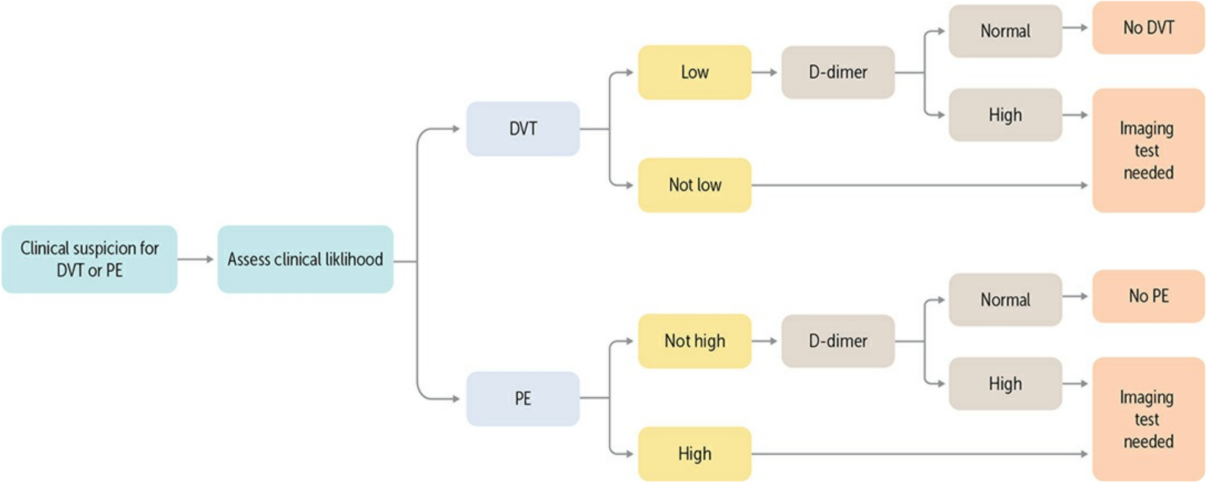

Clinical suspicion for DVT or PE
Assess clinical liklihood
DVT
Low
D-dimer
Normal
No DVT
High
Imaging test needed
Not low
PE
Not high
D-dimer
Normal
No PE
High
Imaging test needed
High

FIGURE 2.1-34. **Management of suspected DVT based on Wells’ score.** (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

- D-dimer is sensitive but not specific for DVT (elevated in many other clinical situations

such as infection, malignancy, pregnancy, and postoperative states, to name a few).
- Therefore a ⊖ D-dimer test can be used to rule out the possibility of VTE in low-risk patients.

Treatment

- Anticoagulate with subcutaneous LMWH, a direct oral anticoagulant (DOAC), or IV unfractionated heparin followed by oral warfarin or DOACs for a total of 3 months (total duration dependent on cause, number of occurrences, and bleeding risk).
- First-occurrence unprovoked DVT or provoked DVT by a reversible risk factor is unlikely to recur and only requires 3 months of anticoagulation treatment.
- DVT secondary to cancer or a second unprovoked DVT is likely to recur and requires indefinite anticoagulation treatment (extended therapy).
- In patients with contraindications for anticoagulation, inferior vena cava filters should be placed.
- Hospitalized patients should receive DVT prophylaxis consisting of exercise as tolerated, antithromboembolic stockings, and subcutaneous LMWH or unfractionated heparin.
- Catheter-directed thrombolysis is sometimes used as an adjunct to anticoagulation in order to help prevent postthrombotic (postphlebitis) syndrome in patients with low bleeding risk who have a decent life expectancy.

KEY FACT

Extended anticoagulation therapy (no scheduled stop date) for the treatment of DVT is based on bleeding risk and underlying cause of DVT; those who are at low risk of bleeding may be candidates for extended therapy and should receive scheduled (eg, annual) reassessments of risk of bleeding to reassess risks/benefits of continuing therapy.

KEY FACT

Provoked DVT: DVT thought to be caused by an identifiable risk factor such as a recent hospital admission/surgery, beginning estrogen therapy, pregnancy, a long flight, etc.

Unprovoked DVT: No known identifiable cause; possibly due to hereditary factors.

POSTTHROMBOTIC (POSTPHLEBITIC) SYNDROME

Chronic venous insufficiency that develops after a patient has a DVT, which develops into sometimes severe symptoms that impair quality of life. Thought to be due to long-standing venous hypertension from a combination of venous valvular incompetence leading to reflux and thrombotic obstruction.

Risk factors: Preexisting venous insufficiency, old age, obesity, varicose veins, recurrent ipsilateral DVT, symptomatic DVT, iliofemoral (proximal) DVT, and residual thrombus within the first 6 months after thrombotic episode.

History/PE

- Extremity pain and sensation of “heaviness”
- Venous dilation

- Skin pigmentation/phlegmasia, trophic skin changes/stasis dermatitis, venous ulcers (when severe)
- Edema

Diagnosis

Diagnosis is made clinically in patients with a history of DVT and obvious symptoms of chronic venous insufficiency. Imaging modalities such as ultrasound can help identify underlying venous valvular insufficiency and residual clot burden, and blood tests can help elucidate potential underlying clotting disorders.

Treatment

- Conservative management (first line): exercise, compression therapy (compressive stockings), skin care (eg, moisturizers for dry/pruritic skin)
- Venous intervention (eg, endovascular catheter-directed thrombolysis, stenting, surgical correction of venous reflux) for acute clot

PERIPHERAL ARTERIAL DISEASE

Defined as a restriction of the blood supply to the extremities by atherosclerotic plaque. The lower extremities are most commonly affected. Clinical manifestations depend on the vessels involved, the extent and rate of obstruction, and the presence of collateral blood flow.

History/PE

- Presents with intermittent claudication; reproducible cramping pain in the calf, thigh, or buttock after walking for a certain distance (claudication distance) and is relieved with rest.
- As the disease progresses, it causes critical limb ischemia. Pain occurs at rest and affects the distal extremities. Dorsal foot ulcerations may develop secondary to poor perfusion. A painful, cold, numb foot is characteristic of critical limb ischemia (chronic limb-threatening ischemia).
- For more proximal lesions, there will be claudication and weak pulses below the area of occlusion (ie, aortoiliac disease [Leriche syndrome] is characterized by the triad of hip, thigh, and buttock claudication; impotence; and symmetric atrophy of bilateral lower extremities).
- Capillary filling of >15 seconds is seen in severe ischemia.

KEY FACT

Critical limb ischemia (chronic limb-threatening ischemia): Presence of PAD in combination with pain at rest, gangrene, or a lower limb ulceration >2 weeks duration

- **Acute ischemia:**
  - May be due to thrombosis in situ (most common), emboli (usually of cardiac origin), graft/angioplasty occlusion, or trauma. Acute occlusions commonly occur at bifurcations distal to the last palpable pulse (see mnemonic for signs and symptoms).
  - May also be secondary to cholesterol atheroembolism (“blue toe syndrome”), which is characterized by blue toes, livedo reticularis, and renal failure (often secondary to catheterization).

- **Chronic ischemia:** Lack of blood perfusion leads to muscle atrophy, pallor, loss of sweat and sebaceous glands, cyanosis, hair loss, and gangrene/necrosis.

MNEMONIC

The 6 Ps of acute ischemia—

Pain
Pallor
Paralysis
Pulse deficit
Paresthesias
Poikilothermia

KEY FACT

Rest pain seen with an ABI <0.4. (normal ABI: 1.0–1.4)

Diagnosis

- Identify cardiovascular risk factors, especially smoking, diabetes, HTN, and hyperlipidemia.
- **Best initial test:** Ankle-brachial index (ABI) test (1–1.4 is normal); can provide objective evidence of atherosclerosis (≤0.9 is highly sensitive and specific for PAD, rest pain usually occurs with an ABI <0.4).
- **Doppler ultrasound:** Identifies stenosis and occlusion. Normal ankle Doppler readings are >90% of brachial readings.
- **Most accurate test:** Angiography (invasive); computed tomography angiography (CTA) with runoff (noninvasive); often not necessary unless revascularization is indicated.

KEY FACT

Calf claudication = femoral disease
Buttock claudication = iliac disease
Buttock claudication + impotence = Leriche syndrome (aortoiliac occlusive disease)

Treatment

- Treat acute symptomatic ischemia with heparin and prompt revascularization.
- Smoking cessation (vital); optimally treat HTN, hyperlipidemia, and diabetes.
- Educate regarding careful hygiene and foot care. Exercise helps develop collateral circulation.
- Antiplatelet agents (ASA or vorapaxar) do not consistently reduce symptoms but ↓ the risk for associated cardiovascular mortality.
- Cilostazol is effective medication in intermittent claudication, although it is contraindicated in those with CHF.
- Surgery (arterial bypass), percutaneous transluminal angioplasty, and stenting or amputation can be employed when conservative treatment fails or in acute limb ischemia.

KEY FACT

The major cause of mortality in patients with PAD is cardiovascular disease (MI, stroke); there is a 20% to 30% risk for these complications. There is only a 1% to 2% risk for developing limb ischemia.

LYMPHEDEMA

A disruption of the lymphatic circulation that results in peripheral edema and chronic infection of the extremities. Primary (or congenital) lymphedema is rare. Most often caused secondarily by surgeries involving lymph node dissection or, in developing countries, parasitic infections.

History/PE

History will differ by cause. Examples include the following:

- Postmastectomy patients present with unexplained swelling of the upper extremity (secondary to surgery).
- Patients originating from developing countries present with progressive swelling of the lower extremities bilaterally with no cardiac abnormalities (ie, filariasis infection).
- Children present with progressive, bilateral swelling of the extremities (primary).
- Patients with Turner syndrome will have lymphatic edema.

Diagnosis

Diagnosis is clinical. Rule out other causes of edema, such as cardiac/metabolic disorders and DVT.

Treatment

- Directed at symptom management, including exercise, massage therapy, and pressure garments to mobilize and limit fluid accumulation.
- Diuretics are ineffective and relatively contraindicated.
- Maintain vigilance for cellulitis with prompt gram ⊕ antibiotic coverage for infection.

SYNCOPE

Syncope is defined as a transient loss of consciousness (TLOC) secondary to cerebral hypoperfusion. It is characterized by a rapid onset, short duration, and spontaneous complete recovery. It may be cardiac, neurocardiogenic (reflex), orthostatic, or due to other rare causes (Figs. 2.1-35 and 2.1-36, Table 2.1-29). Syncope should be differentiated from other causes of loss of consciousness such as epileptic seizure, hypoglycemia, SCD, and psychogenic causes that are not mediated by cerebral hypoperfusion.

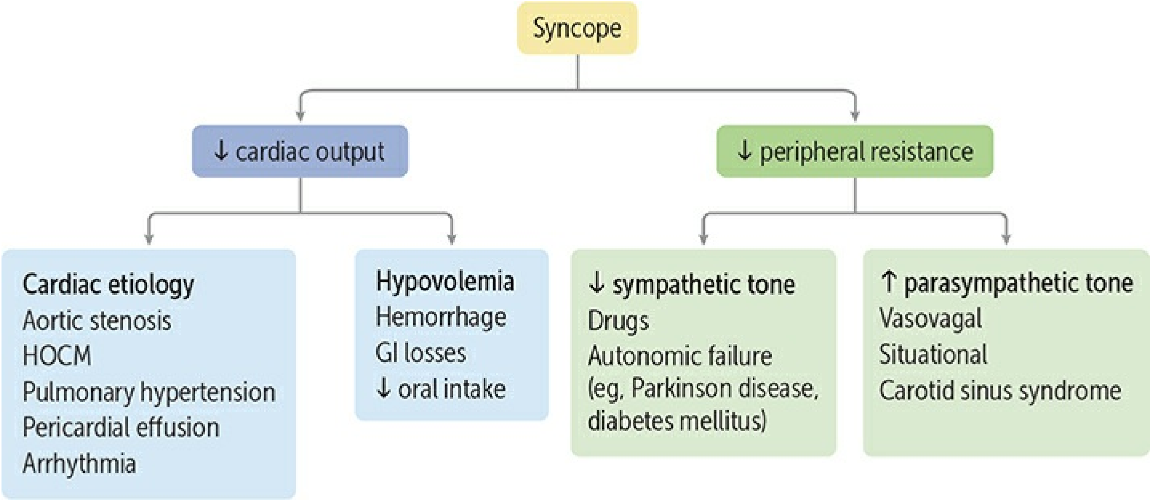

Syncope
↓ cardiac output
↓ peripheral resistance
Cardiac etiology
Aortic stenosis
HOCM
Pulmonary hypertension
Pericardial effusion
Arrhythmia
Hypovolemia
Hemorrhage
GI losses
↓ oral intake
↓ sympathetic tone
Drugs
Autonomic failure
(eg, Parkinson disease, diabetes mellitus)
↑ parasympathetic tone
Vasovagal
Situational
Carotid sinus syndrome

FIGURE 2.1-35. **Pathophysiologic basis of syncope classification.** (Reproduced with permission from USMLE-Rx.com.)

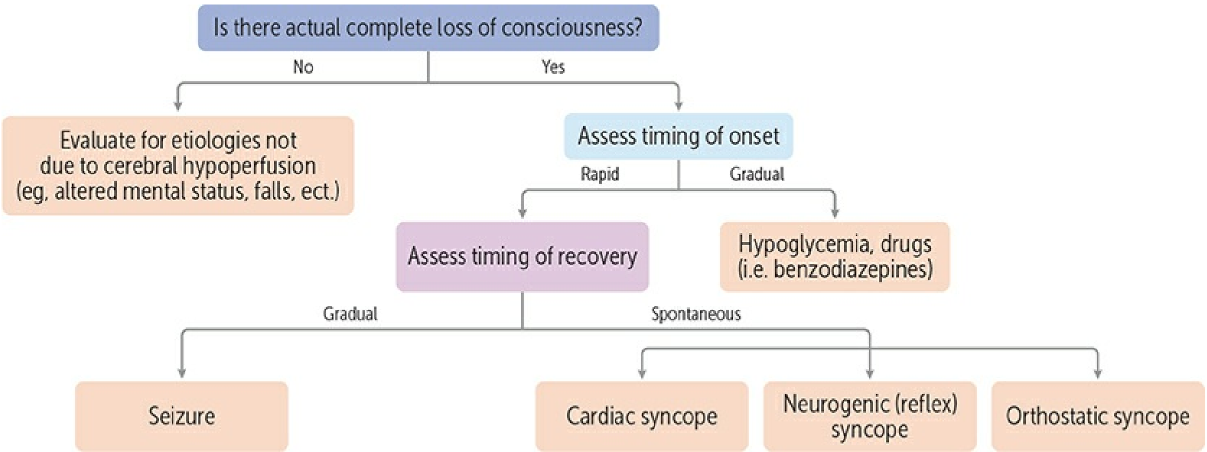

Is there actual complete loss of consciousness?
No
Yes
Evaluate for etiologies not due to cerebral hypoperfusion (eg, altered mental status, falls, ect.)
Assess timing of onset
Rapid
Gradual
Assess timing of recovery
Hypoglycemia, drugs (i.e. benzodiazepines)
Gradual
Spontaneous
Seizure
Cardiac syncope
Neurogenic (reflex) syncope
Orthostatic syncope

FIGURE 2.1-36. **Approach to diagnosis of syncope.** (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.1-29. **Selected Syncope Syndromes**

PATIENT PRESENTATION	MOST LIKELY DIAGNOSIS	WORKUP	MANAGEMENT
NEURALLY MEDIATED (REFLEX) SYNCOPE			

Syncope after wearing tight collar/tie, shaving, or neck movements (carotid stimulation)	Carotid sinus syndrome	If diagnosis is highly likely:
		■ No further evaluation is needed (ie, treat directly)
		If diagnosis unclear:
		■ Investigations to consider:
		■ Carotid sinus massage (for carotid sinus syndrome)
		■ Tilt-table testing (for situation and vasovagal syncope)
		■ Rule out other serious causes of syncope (eg, cardiac)
			Predictable onset or low-recurrence syncope:
			■ Patient education, reassurance, and avoidance of triggers
			■ Increased fluid intake and salt intake
			Unpredictable onset or high-recurrence syncope:
			■ Consider specific associations and treat; some examples follow:
			  ■ Low BP: Consider fludrocortisone, midodrine; stop or reduce hypotensive drugs
			  ■ Prodromes: Counterpressure maneuvers (ie, handgrip, arm tensing or leg crossing maneuvers) or tilt training (physical therapy to improve orthostatic tolerance)
			  ■ Treatment of arrhythmias based on loop recorder findings (eg, permanent pacing for significant cardiac inhibition; asystolic pause >3 seconds)

Syncope on coughing/defecation/urination	Situational		
Syncope associated with fear, noxious stimuli, heat exposure, prolonged standing	Vasovagal		

PATIENT PRESENTATION	MOST LIKELY DIAGNOSIS	WORKUP	MANAGEMENT
ORTHOSTATIC SYNCOPE			
Syncope on change in body posture with history of drug use that is associated with orthostasis (eg, alcohol, vasodilators, diuretics, phenothiazine, antidepressants)	Volume depletion	Orthostatic challenge: Change in BP from supine to erect posture can be evaluated in several ways: ■ Active standing test ■ Head-up tilt-table test ■ 24-hour ambulatory BP monitoring (ABPM) may allow assessment of BP with changes in postures or on performing maneuvers Autonomic function: To detect autonomic failure as cause: ■ Valsalva maneuver ■ Deep breathing test: Reduced variability in HR may suggest autonomic dysfunction ■ 24-hour ABPM	■ Education and reassurance ■ Expansion of extracellular volume: Maintain hydration, avoid extreme heat, increased sodium intake ■ Stop or reduce antihypertensive treatments ■ Counterpressure maneuvers when warning symptoms are present ■ Compression stockings or abdominal binders (to increase venous return) ■ Head-up tilt sleeping >10 degrees (prevents nocturnal polyuria, maintains better distribution of body fluids, and ameliorates nocturnal hypertension) ■ Medications: Midodrine (first line in chronic autonomic failure, increases BP), fludrocortisone (expands volume), β-blockers, pyridostigmine, clonidine
Syncope with volume loss such as hemorrhage, diarrhea, vomiting Syncope with neurologic diseases such as pure autonomic failure, multiple system atrophy, Parkinson disease, or dementia with Lewy bodies	Primary autonomic failure		
Syncope with history of diabetes, amyloidosis, spinal cord injuries, autoimmune autonomic neuropathy, paraneoplastic autonomic neuropathy, kidney failure	Secondary autonomic failure		
A young woman with history of tachycardia on assuming upright posture, mental clouding, chronic fatigue, and other systemic symptoms presents with syncope on change in body posture; there is no orthostatic hypotension	Postural tachycardia syndrome (POTS) Note: Most patients with POTS present without syncope	■ Exclude cardiomyopathy or pheochromocytoma ■ ECG, 24-hour Holter monitoring	In addition to treatments mentioned earlier, consider exercise reconditioning

Classification

- **Cardiac syncope:** Unstable tachyarrhythmias, bradyarrhythmias, or structural disease (eg, HOCM, aortic stenosis, aortic dissection, cardiac tamponade) may cause cerebral hypoperfusion and syncope. They are discussed in detail in their relevant sections.
- **Neurally mediated (reflex):** There is generally a trigger (eg, carotid stimulation) that induces cardiovascular reflexes, instigating either hypotension or bradycardia or both. Examples include carotid sinus syndrome, situational, and vasovagal syncope (see Table 2.1-29).
- **Orthostatic:** Orthostatic syncope is due to venous pooling that occurs on changing from a supine to an upright posture. Volume depletion or failure of arterial baroreceptors to provoke vasoconstriction of the systemic resistance vessels results in a dip in BP and syncope. Causes include drugs, postural tachycardia syndrome, volume depletion, and primary/secondary autonomic failure (see Table 2.1-29).

KEY FACT

Vasovagal is the most common etiology of syncope.

History/PE

- Age, triggers, prodromal symptoms, and associated symptoms should be investigated. Family history should be elucidated (HOCM, LQTS).
- Syncope can be confused with seizures. Unlike syncope, seizures may be characterized by a preceding aura, tonic-clonic activity, tongue-biting, bladder and bowel incontinence, and a postictal phase (ie, recovery is gradual).
- Presentation of key syncope syndromes is shown in Table 2.1-29.

KEY FACT

Red flags with syncope include onset with exertion, chest pain, dyspnea, palpitations, severe headache, focal neurologic deficits, diplopia, ataxia, dysarthria, low back pain, or family history of SCD.

Diagnosis

Initial syncope evaluation includes history, physical examination (including supine and standing BP), and ECG. Further testing depends on the suspected etiology.

KEY FACT

Cardiac syncope is associated with 1-year SCD rates of up to 40%.

- **Investigations for suspected cardiac causes:**
  - **Arrhythmias:** Holter monitor or 2-week event recorder
  - **Structural heart disease:** Echocardiogram
  - **Ischemia:** Cardiac stress tests to look for ischemia
  - Exercise testing for exertion-induced syncope
- **Investigations for neurally mediated (reflex) and orthostatic syncope:**

  - CSM to assess for carotid sinus hypersensitivity
  - Head-up tilt testing to rule out vasovagal, situational, or orthostatic causes
  - Autonomic function tests (eg, analyzing BP, HR during Valsalva, deep breathing) to identify autonomic failure
- **Other:** Blood tests as indicated (oxygen saturation for hypoxemia, hematocrit for hemorrhage, troponins for ACS, D-dimers for PE)

KEY FACT

Vasovagal is the most common etiology of syncope.

Treatment

Tailored to the etiology.

- Treatment of cardiac arrhythmias and structural cardiac diseases that cause syncope is specific to the underlying condition and is described earlier in the text.
- In patients with unexplained syncope or high risk of SCD (CAD, DCM, HCM, arrhythmogenic right ventricular cardiomyopathy, LQTS, Brugada), consider ICD.
- Treatment of important neurally mediated and orthostatic syncope syndromes is covered in Table 2.1-29.

KEY FACT

Syncope with:

1. Exertion: Aortic stenosis, mitral stenosis, pulmonary hypertension, HOCM, and coronary artery disease.
2. Dysarthria, diplopia, vertigo, neurologic symptoms: TIA or stroke
3. Arm exercise: Subclavian steal syndrome
4. Changing position: Atrial myxoma/thrombus
5. Severe chest/back pain, differential BP in arms: Aortic dissection

NOTES

HIGH-YIELD FACTS IN

DERMATOLOGY

- Layers of the Skin
- Allergic and Immune-Mediated Skin Disorders
  - HYPERSENSITIVITY REACTIONS
  - ATOPIC DERMATITIS (ECZEMA)
  - CONTACT DERMATITIS
  - SEBORRHEIC DERMATITIS
  - PSORIASIS
  - URTICARIA (HIVES)
  - DRUG ERUPTION
  - ERYTHEMA MULTIFORME
  - STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS
  - ERYTHEMA NODOSUM
  - BULLOUS PEMPHIGOID/PEMPHIGUS VULGARIS
  - NUMMULAR ECZEMA
  - PYODERMA GANGRENOSUM
- Infectious Disease Manifestations of the Skin
  - VIRAL DISEASES
  - BACTERIAL INFECTIONS
  - FUNGAL INFECTIONS
  - PARASITIC INFECTIONS
- Ischemic Skin Disorders
  - DECUBITUS ULCERS
  - GANGRENE
- Miscellaneous Skin Disorders
  - STASIS DERMATITIS
  - ACANTHOSIS NIGRICANS
  - LICHEN PLANUS
  - ROSACEA
  - PITYRIASIS ROSEA
  - VITILIGO
  - EYELID LESIONS
  - EPIDERMAL INCLUSION CYSTS
  - DERMATOFIBROMA
  - HIDRADENITIS SUPPURATIVA
  - ICHTHYOSIS VULGARIS
  - AGE-RELATED SKIN CHANGES
  - SUN PROTECTION
  - SUNBURN
- Neoplasms of the Skin

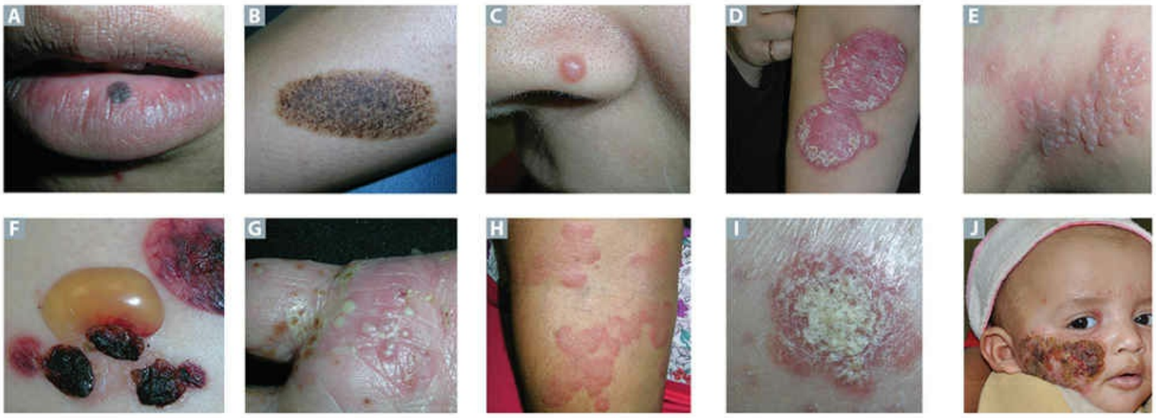
SEBORRHEIC KERATOSIS
ACTINIC KERATOSIS
CUTANEOUS SQUAMOUS CELL CARCINOMA
BASAL CELL CARCINOMA
MELANOMA
KAPOSI SARCOMA
MYCOSIS FUNGOIDES (CUTANEOUS T-CELL LYMPHOMA)
CHERRY ANGIOMAS (HEMANGIOMAS)
INFANTILE HEMANGIOMAS
PYOGENIC GRANULOMA
NECROBIOSIS LIPOIDICA

LAYERS OF THE SKIN

The skin is the largest organ in the human body. It provides a barrier and immunologic protection against the environment; regulates body temperature, fluids, and electrolytes; and allows for touch and sensation. Table 2.2-1 outlines common terminology related to the skin.

TABLE 2.2-1. Dermatologic Macroscopic Terms

LESION	CHARACTERISTICS	EXAMPLES
Macule	Flat lesion <1 cm	Freckle, labial macule (see Image A)
Patch	Flat lesion ≥1 cm	Salmon patch (see Image B)
Papule	Elevated palpable lesion <1 cm	Mole (nevus; see Image C), acne
Plaque	Elevated lesion ≥1 cm	Psoriasis (see Image D)
Vesicle	Fluid-containing blister <1 cm	Chickenpox (varicella), shingles (zoster; see Image E)
Bulla	Fluid-containing blister ≥1 cm	Bullous pemphigoid (see Image F)
Cyst	Epithelium-lined sac containing material or fluid	Pilar cyst (follicular cyst on scalp)
Pustule	Vesicle containing pus	Pustular psoriasis (see Image G)
Wheal	Transient edematous papule or plaque	Hives (urticaria; see Image H)
Scale	Flaking off of stratum corneum	Psoriasis (see Image I)
Crust	Exudate of dried serum, blood, and/or pus	Impetigo (see Image J)
Ulcer	Defect extending through the epidermis and upper dermis	Diabetic foot ulcer
Lichenification	Hypertrophy and thickening of the epidermis with accentuation of normal skin markings	Chronic scratching (pruritic scabies, eczema)



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ALLERGIC AND IMMUNE-MEDIATED SKIN DISORDERS

HYPERSENSITIVITY REACTIONS

Figure 2.2-1 illustrates the algorithm for a skin rash workup. Table 2.2-2 outlines information regarding the four types of hypersensitivity reactions.

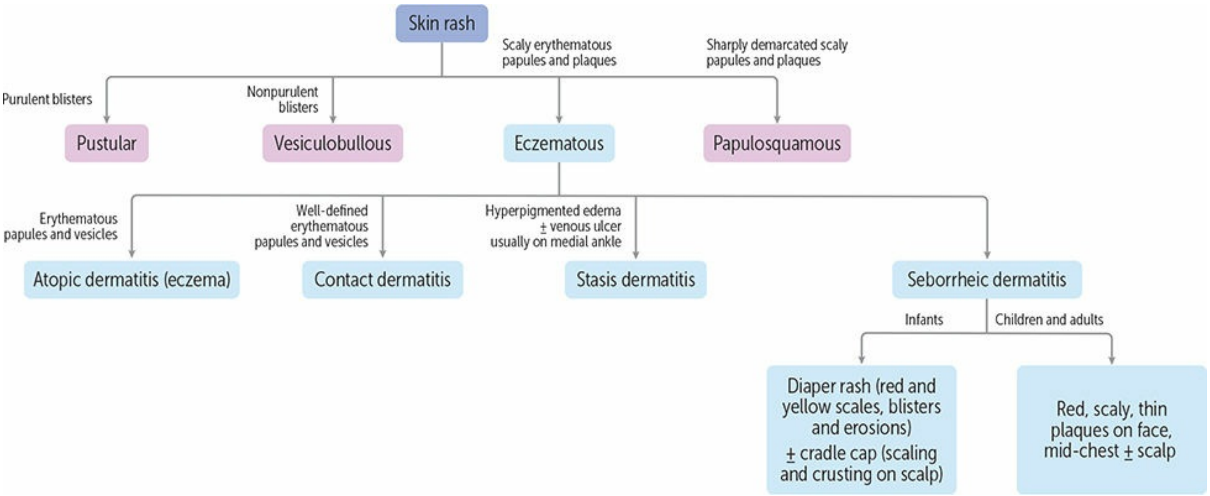
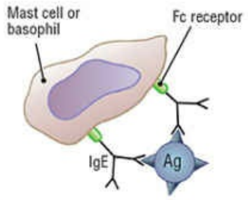
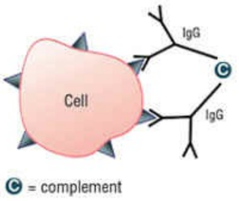
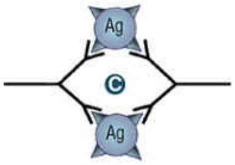
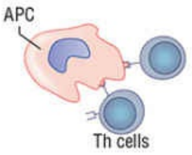

Skin rash
Purulent blisters
Nonpurulent blisters
Scaly erythematous papules and plaques
Sharply demarcated scaly papules and plaques
Pustular
Vesiculobullous
Eczematous
Papulosquamous
Erythematous papules and vesicles
Well-defined erythematous papules and vesicles
Hyperpigmented edema ± venous ulcer usually on medial ankle
Atopic dermatitis (eczema)
Contact dermatitis
Stasis dermatitis
Seborrheic dermatitis
Infants
Children and adults
Diaper rash (red and yellow scales, blisters and erosions) ± cradle cap (scaling and crusting on scalp)
Red, scaly, thin plaques on face, mid-chest ± scalp

FIGURE 2.2-1. **Algorithm for eczematous skin rash workup.** Management depends on the appearance of the rash and the age group affected. Eczematous lesions require further workup to determine the type of dermatitis. (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.2-2. **Types and Mechanisms of Hypersensitivity Reactions**

DESCRIPTION	MECHANISM	COMMENTS	EXAMPLES
TYPE I			
Anaphylactic and atopic 	Antigen cross-links preformed surface-bound IgE on mast cells and basophils, triggering the release of vasoactive amines like histamine Reaction develops rapidly as a result of preformed antibody	**F**irst and **F**ast (like anaphylaxis) Types I, II, and III are all antibody mediated	Anaphylaxis (bee sting, food allergy), asthma, urticaria, urticarial drug reactions, local wheal and flare
TYPE II			
Cytotoxic 	IgM and IgG bind to antigen on an "enemy" cell, leading to lysis by complement or phagocytosis	Cy-2-toxic Antibody and complement lead to formation of the membrane attack complex (MAC)	Autoimmune hemolytic anemia, erythroblastosis fetalis, Goodpasture syndrome, rheumatic fever
TYPE III			
Immune complex 	Antigen-antibody complexes fix complement, which attracts polymorphonuclear neutrophils (PMNs; PMNs release lysosomal enzymes)	Imagine an immune complex as three things stuck together: antigen-antibody-complement Includes many glomerulonephritides and vasculitides	Polyarteritis nodosa, immune complex glomerulonephritis, systemic lupus erythematosus (SLE), rheumatoid arthritis
TYPE IV			
Delayed (cell-mediated) type 	Sensitized T lymphocytes encounter antigen and then release lymphokines (leading to macrophage activation)	Fourth and final (last)—delayed Cell mediated, not antibody mediated; therefore it is not transferable by serum	Tuberculosis (TB) skin tests, transplant rejection, contact dermatitis

APC, Antigen-presenting cell; *Th cells*, T-helper cells. Modified with permission from Le T et al. *First Aid for the USMLE Step 1 2015*. New York, NY: McGraw-Hill Education; 2015.

ATOPIC DERMATITIS (ECZEMA)

A chronic inflammatory dermatitis that classically manifests in infancy and persists into adulthood. It is characterized by epidermal barrier dysfunction (multifactorial; however, likely due to filaggrin deficiency), causing sensitization, which in turn leads to inflammation, pruritus, and ultimately lichenification (Fig. 2.2-2).

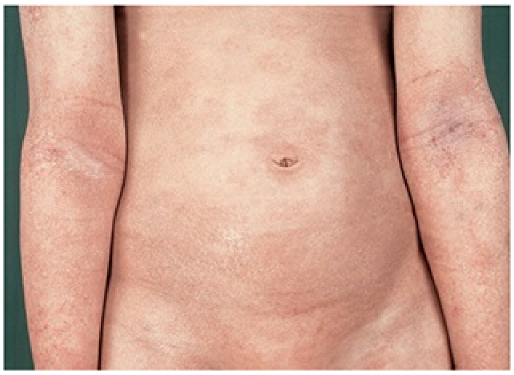


FIGURE 2.2-2. **Atopic dermatitis.** Lichenification, excoriations, and ill-defined, scaly erythematous plaques are characteristic. (Reproduced with permission from Tintinalli JE et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide,* 7th ed. New York, NY: McGraw-Hill; 2011.)

KEY FACT

Long-term use of immunomodulating medications (particularly TNF-α inhibitors) may ↑ the risk for developing lymphoma.

History/PE

- Look for a family history of asthma, eczema, and allergic rhinitis ("atopic triad"), as well as food allergies.
- Patients are at ↑ risk for secondary bacterial (*Staphylococcus aureus* or *Streptococcus pyogenes*) and viral (herpes simplex virus or molluscum) infection due to constant waxing and waning cycles of pruritus and excoriation.
- Triggers include climate, food, skin irritants, and allergens.
- **Manifestations by age group:**
  - **Infants (Fig. 2.2-3):** Erythematous, edematous, weeping, pruritic vesicles, papules, and plaques on the face, scalp, and extensor surfaces of the extremities. The diaper area is often spared.

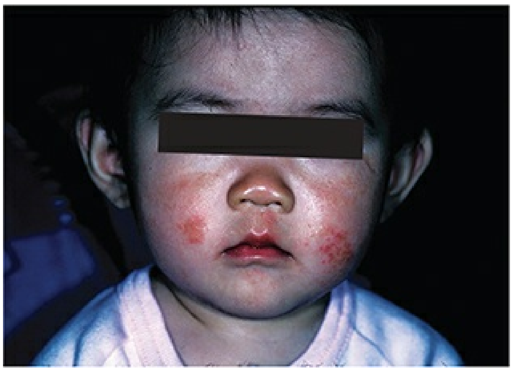


FIGURE 2.2-3. **Atopic dermatitis in an infant.** Characteristic involvement of the face and cheeks, which is not commonly seen in adults. (Reproduced with permission from Dr. Richard Usatine.)

  - **Children:** Dry, scaly, pruritic, excoriated vesicles, papules, and plaques in the flexural areas and neck.
  - **Adults:** Lichenification and dry, fissured skin in a flexural distribution. Often, there is hand, wrist, neck involvement.

Diagnosis

Characteristic exam findings and history are sufficient. Excluding contact dermatitis by history and anatomic distribution is important. Potassium hydroxide (KOH) prep can help distinguish chronic eczema from tinea. Mild peripheral eosinophilia and ↑ IgE may be seen but have no diagnostic value.

KEY FACT

Erythema toxicum neonatorum typically begins 1 to 3 days after delivery and presents with red papules, pustules, and/or vesicles with surrounding erythematous halos. ↑ eosinophils are present in the pustules or vesicles. This benign eruption usually resolves in 1 to 2 weeks with no treatment.

Treatment

- The primary goal of therapy is to break the itch-scratch cycle with agents targeted at inflammation, pruritus, and xerosis (dry skin).
- Topical corticosteroids are first-line therapy for flares, but atrophy, telangiectasias, and rebound flares can occur with prolonged use. Topical calcineurin inhibitors (eg, tacrolimus) are useful as steroid-sparing agents for moderate to severe eczema for patients >2 years of age.
- H_1-blockers may be used for relief of pruritus. A first-generation H_1-blocker (eg, hydroxyzine) would be appropriate for nighttime use.
- Aggressive use of emollients, avoidance of harsh soaps, and limiting hot showers after resolution of acute flares will prevent future episodes. Consider phototherapy and dupilumab treatment.

CONTACT DERMATITIS

A type IV hypersensitivity reaction that results from contact with an allergen to which the patient has previously been exposed and sensitized such as nickel, poison ivy, perfumes/deodorants, and neomycin. More common in adults.

History/PE

- Presents with pruritus and an eczematous rash, with the distribution of the rash often mimicking the contact event (Fig. 2.2-4). Characteristic distributions are seen where makeup, clothing, perfume, nickel jewelry, and plants come into contact with the skin.

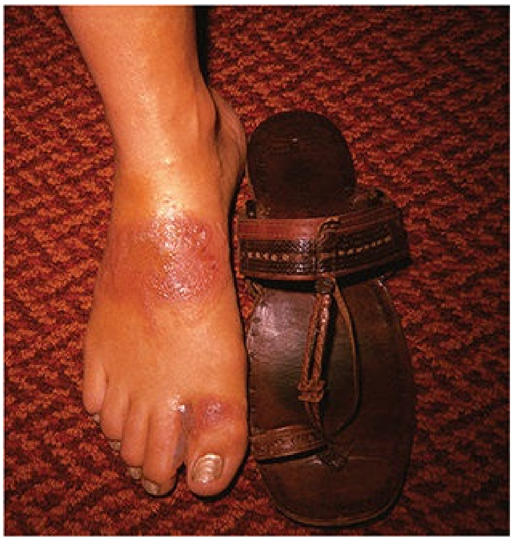


FIGURE 2.2-4. **Contact dermatitis.** Shown are erythematous papules and vesicles with serous weeping localized to areas of contact with the offending agent. (Reproduced with permission from Hurwitz RM. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation*, 2nd ed. Stamford, CT: Appleton & Lange; 1998.)

- Often described as a "linear" or "angular" rash. It can spread over the body via transfer of allergen by the hands or via circulating T lymphocytes.
- **Frequently implicated allergens:** Poison ivy, poison oak, nickel, topical over-the-counter antibiotics, cosmetics, and latex.

Diagnosis

Characteristic exam findings and history are sufficient. Excluding atopic dermatitis (eczema) is important. Patch testing can be used to establish the causative allergen after the acute-phase eruption has been treated.

KEY FACT

Patch testing results are affected by topical steroids and calcineurin inhibitors but not by antihistamines, because type IV hypersensitivity reactions are not histamine mediated.

Treatment

The best initial treatment involves topical corticosteroids and allergen avoidance. In severe cases, a systemic corticosteroid may be needed.

SEBORRHEIC DERMATITIS

A common chronic inflammatory skin disease that may be caused by a reaction to *Malassezia furfur*, a generally harmless yeast found in sebum and hair follicles. It has a predilection for areas with sebaceous glands such as the eyebrows, nasolabial folds, and posterior ears.

History/PE

Rash presentation varies with age:

- **Infants:** Severe, red diaper rash with yellow scale, erosions, and blisters. Scaling and crusting ("cradle cap") may be seen on the scalp (see Fig. 2.2-5A).

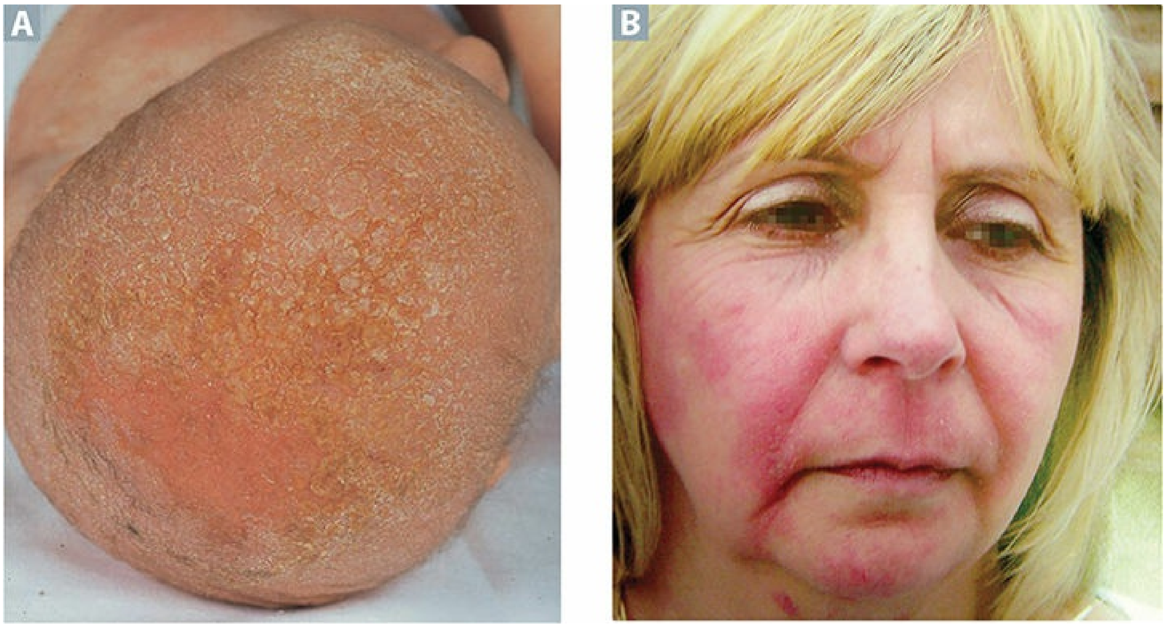


FIGURE 2.1-5. **Seborrheic dermatitis. (A)** Seborrheic dermatitis (cradle cap) in an infant. Note the yellow, scaly crust present on the infant's scalp with an area of erosion. **(B)** Photo-exacerbated seborrheic dermatitis, affecting the face only at sites of predilection for the seborrheic eruption. (A reproduced with permission from Tintinalli JE et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide,* 7th ed. New York, NY: McGraw-Hill; 2011. B reproduced with permission from Gold-smith LA et al. *Fitzpatrick's Dermatology in General Medicine,* 8th ed. New York, NY: McGraw-Hill; 2012.)

- **Children/adults:** Ill-defined red, scaly, thin plaques are seen around the ears, eyebrows, nasolabial fold, midchest, and scalp (see Fig. 2.2-5B).
- **Patients with HIV/AIDS, psychotic disorders, and Parkinson disease** can develop severe, widespread seborrheic dermatitis.

Q

A 23-year-old woman is seen for an itchy, linear rash on her right leg. She returned from a camping trip 4 days ago and denies using any new makeup, clothing, or jewelry. What features of this presentation favor a contact dermatitis?

Diagnosis

Characteristic exam findings and history are sufficient. Can be confused with atopic dermatitis, contact dermatitis, tinea, or psoriasis.

Treatment

Treat adults with ketoconazole, selenium sulfide, or zinc pyrithione shampoos for the scalp and topical antifungals (ketoconazole cream) and/or topical corticosteroids for other areas. Cradle cap often resolves with routine bathing and application of emollients in infants.

PSORIASIS

A T-cell–mediated inflammatory dermatosis characterized by well-demarcated, erythematous plaques with silvery scales (Fig. 2.2-6A) due to dermal inflammation and epidermal hyperplasia. Psoriasis can begin at any age.

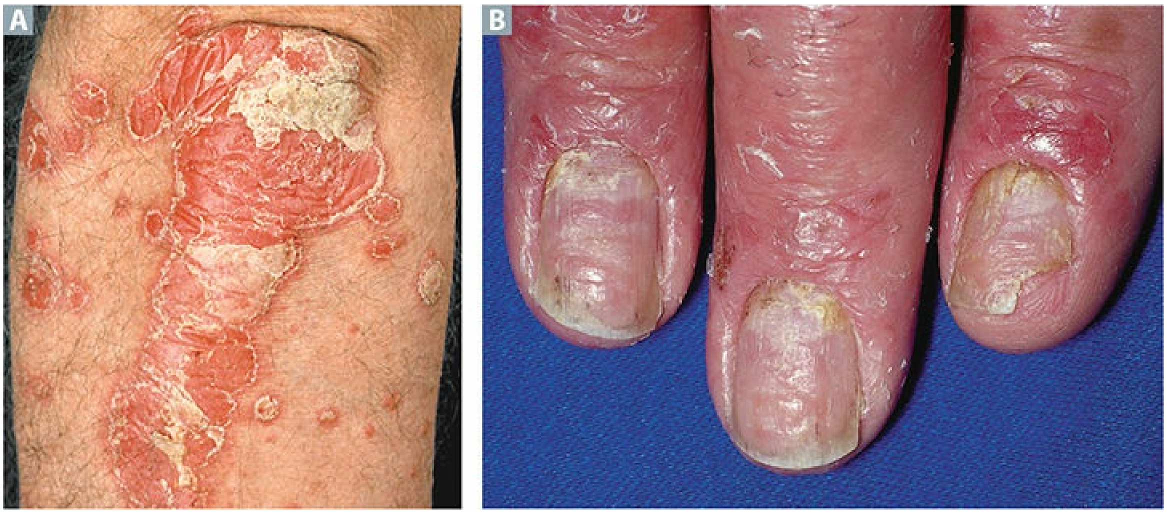


FIGURE 2.2-6. **Psoriasis. (A)** Skin changes. The classic sharply demarcated plaques with silvery scales are commonly located on the extensor surfaces (eg, elbows, knees). **(B)** Nail changes. Note the pitting, onycholysis, and "oil spots." (A reproduced with permission from Wolff K et al. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology,* 7th ed. New York, NY: McGraw-Hill; 2013. B reproduced with permission from Hurwitz RM. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation,* 2nd ed. Stamford, CT: Appleton & Lange; 1998.)

History/PE

- Lesions are classically found on the extensor surfaces, including the elbows and knees. Scalp and lumbosacral regions are often involved. Nails are frequently affected with pitting, "oil spots," and onycholysis (lifting of the nail plate, see Fig. 2.2-6B).
- Lesions initially appear small but may become confluent and can be provoked by local irritation or trauma (Koebner phenomenon). Some medications such as β-blockers, lithium, and angiotensin-converting enzyme (ACE) inhibitors can worsen psoriatic lesions.
- Up to 30% develop psoriatic arthritis (affecting small joints of the hands and feet).

A

The asymmetric involvement of the rash, its linear arrangement (possibly from contact with a plant during the camping trip), and the time from exposure to rash presentation all point to contact dermatitis.

Diagnosis

- Characteristic exam findings and history are sufficient. Classical presentation: Auspitz sign (pinpoint bleeding when scale is scraped) overlying well-demarcated, erythematous plaques with silvery "micaceous" scale.
- Perform a biopsy if diagnosis is uncertain. Histology shows a thickened epidermis, elongated rete ridges, an absent granular cell layer, preservation of nuclei in the stratum corneum (parakeratosis), and a sterile neutrophilic infiltrate in the stratum corneum (Munro microabscesses).

KEY FACT

If a rash involves the extensor surfaces, think psoriasis. If a rash involves the flexor surfaces, think atopic dermatitis.

Treatment

- **Local disease:** Manage with topical steroids, calcipotriene (vitamin D derivative), and retinoids such as tazarotene or acitretin (vitamin A derivative).
- **Severe disease or presence of psoriatic arthritis:** Methotrexate or anti–tumor necrosis factor (TNF) biologics (etanercept, infliximab, adalimumab). Other agents such as ustekinumab (anti-interleukin [IL]-12/23), secukinumab (anti-IL17), and ultraviolet (UV) light therapy can be used for extensive skin involvement, except in immunosuppressed patients who can develop skin cancer from UV light.
- Before starting methotrexate or anti-TNF biologics, patients should, at a minimum, get a complete blood count (CBC), comprehensive metabolic panel (CMP), hepatitis panel, and testing for TB (purified protein derivative [PPD] or interferon gamma release assay [IGRA]).

KEY FACT

"Sausage digits" and pencil-in-cup x-ray findings are suggestive of psoriatic arthritis.

URTICARIA (HIVES)

Results from the release of histamine and prostaglandins from mast cells in a type I hypersensitivity response. Sharply demarcated edematous plaques with surrounding erythema ("wheal and flare") are seen, with each lesion lasting <24 hours. Can be acute or chronic (lasting >6 weeks).

History/PE

- Urticaria lesions (wheals) are erythematous or white transient papules or plaques representing dermal edema. Lesions may be widespread.
- In severe allergic reactions, extracutaneous manifestations can include tongue swelling, angioedema (deep, diffuse swelling often around the eyes and mouth; Fig. 2.2-7), asthma, gastrointestinal (GI) symptoms, joint swelling, and fever.

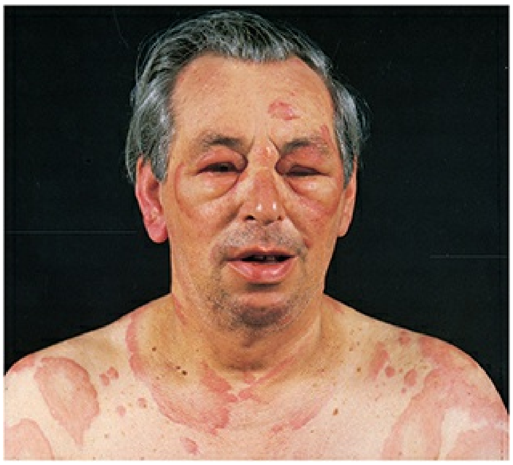


FIGURE 2.2-7. **Urticaria (hives) and angioedema.** This patient has urticaria occurring on the face, neck, and shoulders with orbital angioedema. (Reproduced with permission from Goldsmith LA et al. *Fitzpatrick's Dermatology in General Medicine*, 8th ed. New York, NY: McGraw-Hill; 2012.)

- Acute urticaria is a response to some often-unidentified trigger: food, drug, virus, insect bite, or physical stimulus (cold, heat, sun). Chronic urticaria is usually idiopathic.

Diagnosis

Characteristic exam findings and history are sufficient. Positive dermatographism (formation of wheals where the skin is stroked) may help. If in doubt, drawing a serum tryptase (co-released with histamine from mast cells) can help clinch the diagnosis. It can often be difficult to determine the cause of urticaria.

Treatment

Treat urticaria with systemic antihistamines. Anaphylaxis (rare) requires intramuscular epinephrine, antihistamines, IV fluids, and airway support.

DRUG ERUPTION

Drug eruptions can range from a mild morbilliform rash (most common; Fig. 2.2-8) to the rare but life-threatening toxic epidermal necrolysis (TEN). Maintain a high suspicion for a cutaneous drug reaction in patients who are hospitalized and develop rashes. Drugs can cause all four types of hypersensitivity reactions (Table 2.2-2), and the same drug may cause different types of reactions in different persons.

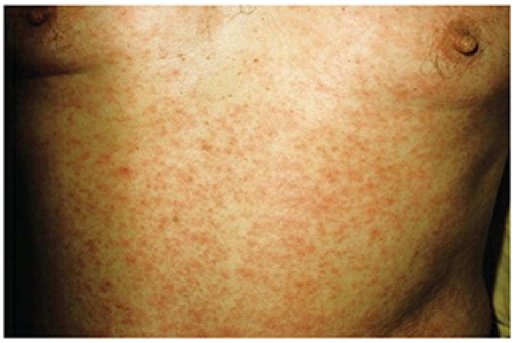


FIGURE 2.2-8. **Morbilliform rash.** Morbilliform rash following drug administration. (Reproduced with permission from Longo DL et al. *Harrison's Principles of Internal Medicine,* 18th ed. New York, NY: McGraw-Hill; 2011.)

KEY FACT

Patients with drug eruptions often have peripheral eosinophilia and eosinophils on histopathology.

History/PE

- Non-anaphylactoid eruptions usually occur 7 to 14 days after exposure: If a patient reacts within 1 to 2 days of starting a new drug, it is probably not the causative agent.
- Eruptions are generally widespread, relatively symmetric, and pruritic.
- Most disappear within 1 to 2 weeks following removal of the offending agent.
- Extreme complications of drug eruptions include erythroderma, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and TEN.

Diagnosis

Characteristic exam findings and history are sufficient. Excluding other causes is important, including viral exanthema, graft-versus-host disease, and autoimmune dermatoses. A skin biopsy may be helpful if the diagnosis is not clear.

Treatment

Discontinue the offending agent; treat symptoms with antihistamines and topical steroids to relieve pruritus. In severe cases, systemic steroids and/or IV immunoglobulin (IVIG) may be used.

ERYTHEMA MULTIFORME

Erythema multiforme (EM) is a cutaneous reaction pattern with classic targetoid lesions (Fig. 2.2-9) that has many triggers and is often recurrent. Herpes simplex is the most common agent.

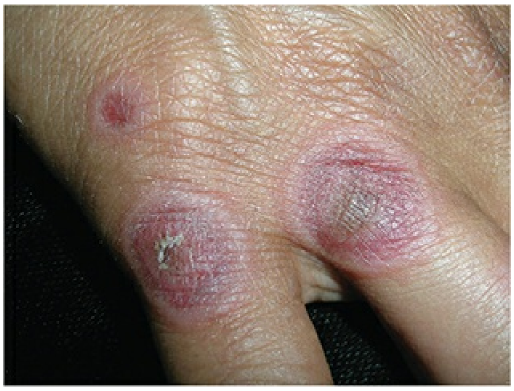


FIGURE 2.2-9. **Erythema multiforme.** (Reproduced with permission from Dr. Richard Usatine.)

History/PE

- Initially, lesions start as erythematous, dusky macules that develop into the characteristic target lesion that commonly affects the palms and soles. The target lesions are described as a central, dusky blister surrounded by a pale edematous ring with a peripheral halo of erythema. The palms, soles, and lips are often affected.
- EM minor is uncomplicated and localized to the skin.
- EM major involves mucous membranes. It is a distinct entity from SJS, and there is no risk for progression to TEN.
- May have systemic symptoms, including fever, myalgias, arthralgias, and headache.

KEY FACT

EM is often triggered by infections such as HSV or mycoplasma. SJS and TEN are typically caused by drugs. Both are type IV hypersensitivity reactions.

Diagnosis

Characteristic exam findings and history are sufficient. As opposed to SJS or TEN, in EM the Nikolsky sign is ⊖.

Treatment

- Symptomatic treatment is all that is necessary; systemic corticosteroids are of no benefit.
- EM minor can be managed supportively; EM major should be treated as burns.

KEY FACT

A differential diagnosis should always include SJS and TEN if a ⊕ Nikolsky sign is present.

STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS

SJS and TEN constitute two different points on the spectrum of life-threatening exfoliative mucocutaneous diseases that are often caused by a drug-induced immunologic reaction. The epidermal separation of SJS involves <10% of body surface area (BSA), whereas TEN involves >30% of BSA. Mucosal involvement is present in >90% of cases of SJS/TEN.

History/PE

- Exam reveals severe mucosal erosions with widespread erythematous, dusky red or purpuric macules, or atypical targetoid lesions (Fig. 2.2-10). The epidermal lesions often become confluent and show a ⊕ Nikolsky sign (separation of the superficial skin layers with slight rubbing) and epidermal detachment.

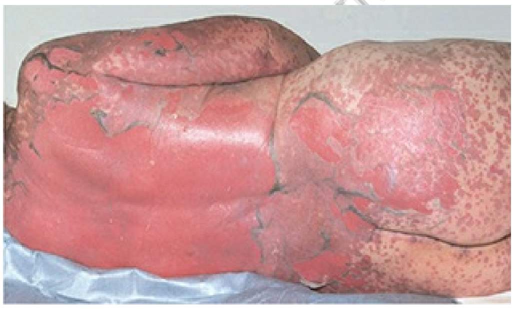


FIGURE 2.2-10. **Toxic epidermal necrolysis.** Note the diffuse erythematous bullae and areas of sloughing secondary to the full-thickness necrosis of the epidermis. (Reproduced with permission from Tintinalli JE et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide,* 7th ed. New York, NY: McGraw-Hill; 2011.)

- Mucous membranes (eyes, mouth, and genitals) often become eroded and hemorrhagic.
- Associated with first-time exposure to drugs: sulfonamides, penicillin, seizure medications (phenytoin, carbamazepine), quinolones, cephalosporins, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs).

Diagnosis

- **SJS/TEN:** Biopsy shows full-thickness eosinophilic epidermal necrosis.
- Differential diagnosis should include staphylococcal scalded-skin syndrome (SSSS), graft-versus-host reaction (usually after bone marrow transplant), radiation therapy, and burns.

KEY FACT

Do not confuse SJS and TEN with SSSS. SSSS is usually seen in children <6 years of age and does not present with targetoid lesions. SJS/TEN is generally seen in adults and is usually caused by a drug rewaction.

Treatment

- High risk for mortality. Early diagnosis and discontinuation of offending agent are critical in improving survival.
- Patients have the same complications as burn victims—thermoregulatory and electrolyte disturbances and secondary infections, so use wound dressings for the skin and manage fluids and electrolytes.
- Data on pharmacologic therapy with steroids, cyclosporine, and IVIG are mixed.

MNEMONIC

Causes of erythema nodosum—NODOSUM

NO cause (60% idiopathic)
Drugs: sulfa, iodides, penicillins
Oral contraceptives
Sarcoidosis
Ulcerative colitis/Crohn disease
Microbiology (TB, leprosy, histoplasmosis, chronic infection)

ERYTHEMA NODOSUM

A panniculitis (inflammatory process of the subcutaneous adipose tissue) triggered by infection (*Streptococcus, Coccidioides, Yersinia*, TB), drugs (sulfonamides, antibiotics, oral contraceptive pills [OCPs]), and chronic inflammatory diseases (sarcoidosis, Crohn disease, ulcerative colitis, Behçet disease).

History/PE

- Painful, erythematous nodules appear on the patient's anterior shins (Fig. 2.2-11) and slowly spread, turning brown or purple. Patients may present with fever and joint pain.

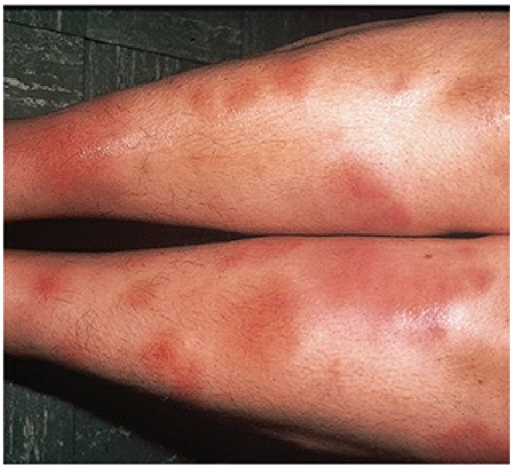


FIGURE 2.2-11. **Erythema nodosum.** Erythematous plaques and nodules are commonly located on pretibial areas. Lesions are painful and indurated but heal spontaneously without ulceration. (Reproduced with permission from Hurwitz RM. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation,* 2nd ed. Stamford, CT: Appleton & Lange; 1998.)

- Patients with erythema nodosum may have a false-⊕ Venereal Disease Research Laboratory result (as in SLE).

Diagnosis

Characteristic exam findings and history are sufficient. A biopsy may help establish the diagnosis. Workup with an ASO titer, PPD in high-risk patients, and CXR to rule out sarcoidosis, or inflammatory bowel disease workup based on the patient's complaints.

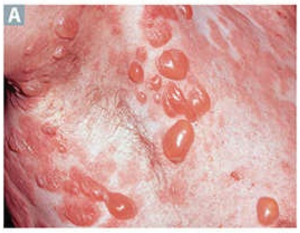
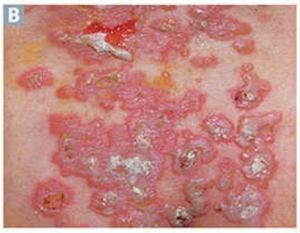
Treatment

Investigate and treat the underlying disease. Cool compresses, bed rest, and NSAIDs are helpful. Potassium iodide may be considered for persistent cases.

BULLOUS PEMPHIGOID/PEMPHIGUS VULGARIS

Table 2.2-3 contrasts the clinical features of bullous pemphigoid with those of pemphigus vulgaris. Fig. 2.2-12 shows the location of antibodies.

TABLE 2.2-3. Acquired, Autoimmune Blistering Dermatoses

VARIABLE	BULLOUS PEMPHIGOID	PEMPHIGUS VULGARIS
Location of blisters	Basement membrane zone	Intraepidermal
Autoantibodies	Against hemidesmosomes (bullous pemphigoid antigens 1 and 2)	Against desmosomes (desmogleins 1 and 3)
Blister appearance	Firm, stable blisters (see Image A); prodromal phase of pruritic eczematous or urticaria-like lesions that precede the development of tense bullae	Erosions are more common than intact blisters (see Image B) because of the lack of keratinocyte adherence
Nikolsky sign	⊖	⊕
Mucosal involvement	Rare	Common
Patient age	Usually >60 years of age	Usually 40–60 years of age
Associated medication triggers	Generally idiopathic	ACE inhibitors, penicillamine, phenobarbital, penicillin
Mortality	Rare	Possible
Diagnosis	Tense bullae on the trunk are indicative of bullous pemphigoid **Most accurate test:** skin biopsy with direct immunofluorescence enzyme-linked immunosorbent assay (ELISA)	Flaccid/unroofed bullae and erosions on the extremities and mucous membranes are indicative of pemphigus vulgaris
Treatment	Topical: High-potency corticosteroids Systemic: Corticosteroid, doxycycline	High-does steroids + immunomodulatory therapy
		

Images reproduced with permission from Wolff K, Johnson RA. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 6th ed. New York, NY: McGraw-Hill; 2009.

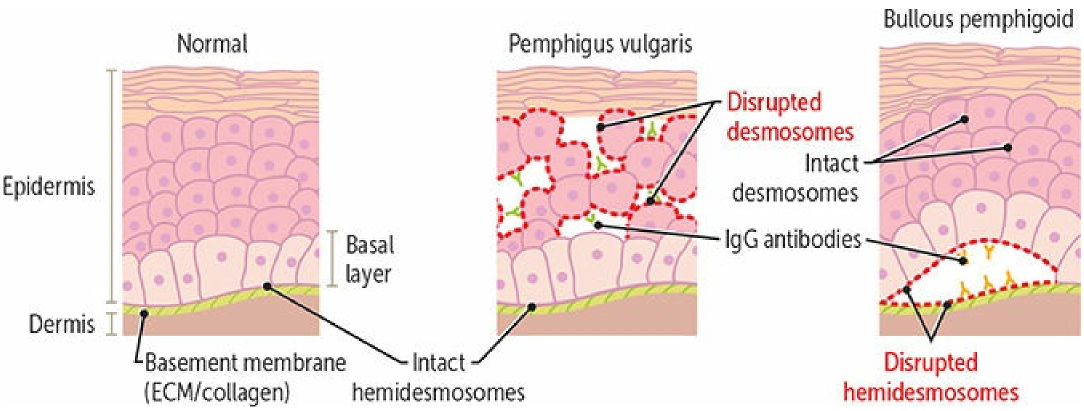

Normal
Pemphigus vulgaris
Bullous pemphigoid
Epidermis
Basal layer
Dermis
Basement membrane (ECM/collagen)
Intact hemidesmosomes
Disrupted desmosomes
Intact desmosomes
IgG antibodies
Disrupted hemidesmosomes

FIGURE 2.2-12. Blistering dermatosis. Compare and contrast the layers of the epidermis in normal skin with the blistering dermatosis. Pemphigus vulgaris involves disruption of desmosomes and shows separation of the stratum spinosum from the stratum basale, causing a "row of tombstones appearance." Bullous pemphigoid involves separation of the epidermis from the dermis due to disruption of hemidesmosomes. (Reproduced with permission from USMLE-Rx.com.)

Q

A 28-year-old Black woman presents to the physician for a new-onset, painful rash. She noticed the erythematous nodules on both lower legs 3 days ago. She has a history of uveitis. What is the next best step to identify the underlying cause of this rash?

NUMMULAR ECZEMA

Chronic relapsing-remitting, pruritic, coin-shaped, scaly plaques (Fig. 2.2-13) most commonly found on the extremities (*nummun* is Latin for coin). While the pathogenesis is unclear, it is thought to be associated with xerosis and decreased skin lipids. Diagnosis is clinical, and treatment includes use of emollients and avoidance of harsh soaps to prevent dry skin and use of topical glucocorticoids.

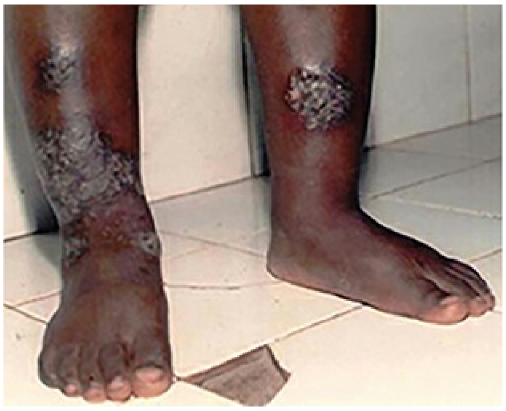


FIGURE 2.2-13. Nummular eczema. (Reproduced with permission from Bissek AC, Tabah EN, Kouotou E, et al. The spectrum of skin diseases in a rural setting in Cameroon (sub-Saharan Africa). *BMC Dermatol.* 2012;12:7. doi:10.1186/1471-5945-12-7.)

PYODERMA GANGRENOSUM

Neutrophilic dermatosis associated with inflammatory bowel disease, rheumatoid arthritis, and underlying malignancy. Presents as papules or pustules that rapidly progress to a painful ulcer with a violaceous border and purulent base (Fig. 2.2-14). Demonstrates pathergy (formation of ulcers at sites of injury). Diagnosis depends on recognizing the clinical presentation and excluding other causes. Treatment involves local or systemic glucocorticoids.

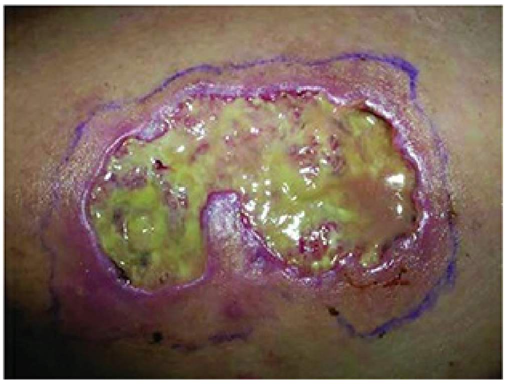


FIGURE 2.2-14. Pyoderma gangrenosum. (Reproduced with permission from Fonder MA, Cummins DL, Ehst BD, et al. Adalimumab therapy for recalcitrant pyoderma gangrenosum. *J Burns Wounds*. 2006;5:e8.)

INFECTIOUS DISEASE MANIFESTATIONS OF THE SKIN

VIRAL DISEASES

Human Herpesviruses

The human herpesviruses (HHVs) are a group of DNA viruses that result in lifelong latent infection and are usually transmitted via physical contact (Table 2.2-4).

TABLE 2.2-4. Human Herpesviruses

VIRUS	HISTORY AND MANIFESTATIONS	DIAGNOSIS	MANAGEMENT
HHV-1 and HHV-2 (herpes simplex viruses)	HHV-1: Transmitted via respiratory/oral secretions. Usually causes oral vesicles and ulcers. Causes temporal lobe encephalitis. HHV-2: Transmitted via sexual contact. Usually manifests as genital lesions. Causes viral meningitis.	Clinical diagnosis should be confirmed by laboratory testing if possible. Vesicles can be unroofed and swabbed—samples can be sent for viral culture or polymerase chain reaction (PCR).	Lesions and other manifestations can be treated or suppressed with acyclovir, valacyclovir, or famciclovir. Choose IV acyclovir for severe infections in immunocompromised, or in cases of central nervous system (CNS) infection.
HHV-3 (varicella-zoster virus [VZV])	The only herpesvirus with airborne transmission. Chickenpox (primary infection) characterized by pruritic vesicles with centrifugal distribution. Severe cases can develop pneumonia, hepatitis, and encephalitis. Shingles (reactivation) presents with vesicular rash that is painful and appears in dermatomal distribution. Can manifest as Ramsay Hunt syndrome (external ear lesions, facial palsy, hearing loss).	VZV lesions can be swabbed and sent for PCR for definitive diagnosis. Samples from other suspected sites of infection (e.g., cerebrospinal fluid [CSF]] in suspected CNS infection, or bronchoalveolar lavage [BAL] fluid in suspected pneumonia) can also be sent for PCR.	Contact and airborne precautions for hospitalized patients with VZV infection or disseminated zoster. Treatment with acyclovir/valacyclovir within 72 hours of rash onset significantly decreases the intensity and duration of pain associated with lesions. IV acyclovir should be used for severe infections. Vaccines are available to prevent primary infection and reactivation.
HHV-4 (Epstein-Barr virus [EBV])	Transmitted via respiratory secretions and saliva. Main cause of infectious mononucleosis (exudative pharyngitis, fever, fatigue, hepatitis, splenomegaly). Associated with development of Burkitt and Hodgkin lymphomas, B- and T-cell lymphomas, nasopharyngeal carcinoma, and posttransplant lymphoproliferative disease.	Infectious mononucleosis can be diagnosed by identifying heterophile antibodies (Monospot test) or IgM against the EBV viral capsid antigen. Blood smear can show atypical lymphocytes.	Treatment is mostly supportive. Patients should avoid contact sports for 4 weeks out of risk of splenic rupture. Note: Maculopapular rash can be seen in cases of infectious mononucleosis that are treated with amoxicillin (ie, when confused with streptococcus-associated pharyngitis).
HHV-5 (cytomegalovirus [CMV])	Transmitted via saliva, sexual contact, blood transfusions, and organ transplants. Can cause CMV mononucleosis (similar to EBV mononucleosis, but with negative Monospot). In the immunocompromised, CMV can cause encephalitis, retinitis, pneumonitis, colitis, hepatitis, and esophagitis ("shallow" ulcers on endoscopy), and cytopenias.	Diagnosis can be made by PCR of samples from affected sites.	IV ganciclovir or oral valganciclovir for treatment.
HHV-6 and HHV-7 (roseoloviruses)	Transmitted via saliva. Can cause roseola infantum in children—high fevers for several days followed by onset of macular rash with centrifugal spread.	Typically a clinical diagnosis.	Self-limited illness.
HHV-8	Transmitted via sexual contact. Associated with Kaposi sarcoma in HIV/AIDS and transplant patients.	No gold standard for diagnosis of HHV-8. Kaposi sarcoma diagnosed by biopsy.	

Herpes Simplex

Painful, recurrent vesicular eruption of the mucocutaneous surfaces due to infection with HSV. Both serotypes can affect both genital and extragenital regions. The virus spreads through epidermal cells, fusing them into giant cells. The local host inflammatory response causes erythema and swelling.

KEY FACT

Dermatitis herpetiformis (DH) has vesicles and erosions like herpes but is NOT caused by HSV. DH consists of symmetric, bilateral pruritic papules, vesicles, bullae, and erosions on the elbows (Fig. 2.2-15), knees, buttocks, neck, and scalp, and it is associated with celiac disease (15%–25%). Treat with dapsone and a gluten-free diet.

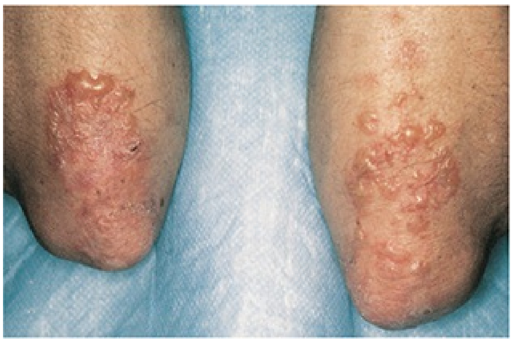


FIGURE 2.2-15. **Dermatitis herpetiformis.** This disorder typically displays pruritic, grouped papulovesicles on elbows, knees, buttocks, and posterior scalp. Vesicles are often excoriated due to associated pruritus. (Reproduced with permission from Longo DL et al. *Harrison's Principles of Internal Medicine*, 18th ed. New York, NY: McGraw-Hill; 2011.)

History/PE

- The initial infection is by direct contact with oral or genital fluids; after the primary episode, the virus remains dormant in local nerve ganglia: HSV-1 in the trigeminal ganglia and HSV-2 in sacral ganglia. First episodes are generally longer and more severe than recurrences.
- Onset is preceded by prodromal tingling, burning, or pain but can also present with lymphadenopathy, fever, discomfort, malaise, and edema of involved tissue.
- Recurrences are limited to mucocutaneous areas innervated by the involved nerve:
  - **Recurrent oral herpes (HSV-1):** The common "cold sore," or herpes labialis, which presents as a cluster of crusted vesicles on an erythematous base (Fig. 2.2-16A). Often triggered by stress, sunlight, or infections.

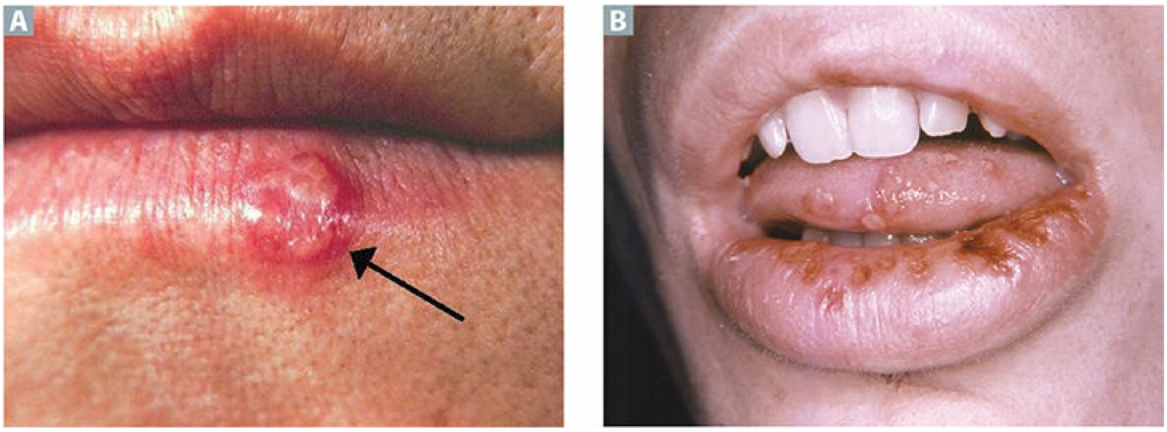


FIGURE 2.2-16. **Herpes simplex. (A)** Herpes labialis. **(B)** HSV-1 lesions of the oral mucosa and tongue. (Image A reproduced with permission from the US Department of Health and Human Services and Dr. Herrmann. Image B reproduced with permission from the US Department of Health and Human Services and Robert E. Sumpter.)

  - **Recurrent genital herpes (HSV-2):** Unilateral and characterized by a cluster of ulcers on an erythematous base, but with less pain and systemic involvement than the primary infection.

A

X-ray of the chest (CXR) to look for bilateral hilar adenopathy, which is suggestive of sarcoidosis. Erythema nodosum is the most common nonspecific cutaneous manifestation of sarcoidosis, after cutaneous sarcoidosis.

Diagnosis

- Clinical diagnosis: Grouped vesicles on an erythematous base.
- **Most accurate test:** Viral culture or PCR test of lesion. Direct fluorescent antigen is the most rapid test.
- Classic multinucleated giant cells on Tzanck smear (see Fig. 2.2-16B) support the diagnosis.

Treatment

- **First episode:** Immunocompetent patients with small lesions only need supportive therapy, but acyclovir, famciclovir, or valacyclovir may be given to speed healing and reduce viral shedding.
  - Immunocompromised patients or those with a severe painful outbreak should receive an antiviral drug within 72 hours of the start of the outbreak.

KEY FACT

Herpetic whitlow presents as painful blisters/sores on the hand resembling “dew drops on a rose.” It is common in healthcare workers, respiratory therapists, dentists, and dishwashers.

- **Recurrent episodes:** Minor lesions can be managed supportively. Acyclovir, famciclovir, or valacyclovir can be given during the episode to reduce healing time by ~2 days.
- **Severe frequent recurrences (>6 outbreaks per year):** Daily prophylaxis with acyclovir, famciclovir, or valacyclovir.
- In patients with AIDS, HSV can persist, with ulcers remaining resistant to antiviral therapy. Symptomatic HSV infection lasting >1 month can be considered an AIDS-defining illness.

Varicella-Zoster Virus

VZV causes two different diseases—varicella and herpes zoster—with transmission occurring via respiratory droplet or by direct contact. VZV has an incubation period of 10 to 20 days, with contagion beginning 24 hours before the eruption appears and lasting until lesions have crusted.

History/PE

Varicella:

- A prodrome of malaise, fever, headache, and myalgia occurs 24 hours before the rash.
- Pruritic lesions appear in crops over 2 to 3 days, evolving from red macules to vesicles that then crust over.
- At any given time, patients may have all stages of lesions present. The trunk, face, scalp, and mucous membranes are involved.
- In adults, chickenpox is often more severe, with systemic complications such as pneumonia and encephalitis.

Zoster:

- Herpes zoster (shingles) represents the recurrence of VZV in a specific nerve, with lesions appearing along the nerve's dermatomal distribution. Outbreaks are usually preceded by intense local pain (acute herpetic neuralgia) followed by grouped blisters on an erythematous base (Fig. 2.2-17). Zoster can become disseminated in immunocompromised persons.

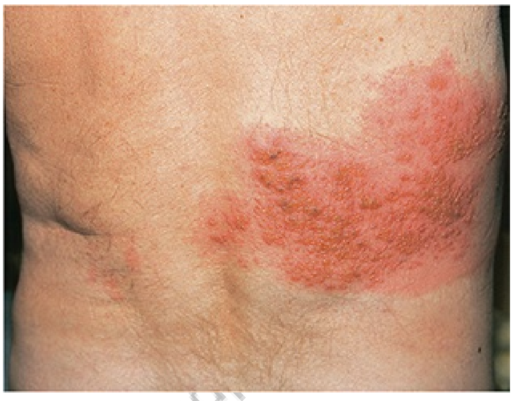


FIGURE 2.2-17. **Varicella zoster.** The unilateral dermatomal distribution of the grouped vesicles on an erythematous base is characteristic. (Reproduced with permission from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York, NY: McGraw-Hill; 2005.)

- Acute herpetic neuralgia: Pain persisting less than 30 days from rash onset.
- Subacute herpetic neuralgia: Pain persisting longer than 30 days but less than 4 months from rash onset.
- Postherpetic neuralgia: Pain persisting greater than 4 months from rash onset.
- Herpes zoster oticus (Ramsay Hunt syndrome): Reactivation of VZV in the geniculate ganglion affecting cranial nerves (CNs) VII and VIII. Presents with shingles in the ear canal and pinna; CN VII involvement causes facial paralysis, and CN VIII involvement causes vertigo and sensorineural hearing loss.
- Herpes zoster ophthalmicus: Reactivation of VZV along trigeminal nerve distribution. Presents with shingles in the trigeminal nerve distribution of V1, herpes zoster keratitis. This is a medical emergency, as it can cause blindness.
- Older patients with zoster can develop postherpetic neuralgia (severe nerve pain that persists for >4 months at the infection site after rash onset).

Diagnosis

PCR or viral culture test of lesion. Characteristic exam findings and history.

Treatment

- Varicella is self-limited in healthy children. A live attenuated vaccine is available that should be given to children in two doses at ages 1 and 4. Also recommended for adults over 60 years of age. May be given to HIV patients with CD4+ cell count >200.

- Adults should be treated with systemic acyclovir to treat symptoms and prevent complications. Pain control with NSAIDs for acute and subacute herpetic neuralgia and neuropathic agents (gabapentin, pregabalin, tricyclic antidepressants) for postherpetic neuralgia.
- Postexposure prophylaxis is rarely needed, as most patients in the United States have been vaccinated or had childhood varicella. If needed, immunocompromised individuals, pregnant women, and newborns should receive varicella-zoster immune globulin within 10 days of exposure. Immunocompetent adults should receive a varicella vaccine within 5 days of exposure.

Complications

Herpes zoster ophthalmicus, herpes zoster oticus (Ramsay Hunt syndrome), and congenital varicella syndrome.

Molluscum Contagiosum

A poxvirus infection that is most common in young children and in AIDS patients. It is spread by direct skin-to-skin contact (sports, sex) or sharing infected clothing or towels.

History/PE

- Presents as tiny, flesh-colored, dome-shaped, waxy papules, frequently with central umbilication. In children, lesions are found on the trunk, extremities, or face (Fig. 2.2-18). In adults, they are considered sexually transmitted infections (STIs) and are commonly found on the genitalia and in the perineal region. Typically spares palms and soles.

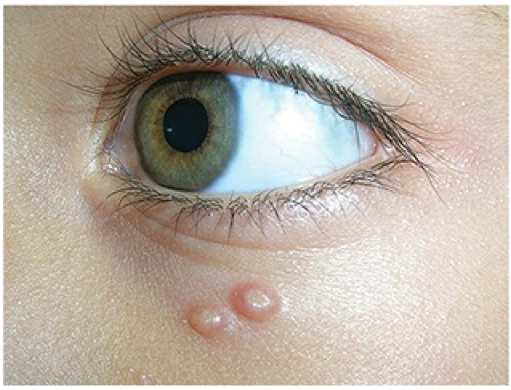


FIGURE 2.2-18. **Molluscum contagiosum.** Flesh-colored, dome-shaped papules present on the face of an adolescent. (Reproduced with permission from Dr. Richard Usatine.)

- Lesions are asymptomatic unless they become inflamed or irritated.

Diagnosis

- Characteristic exam findings and history are sufficient.
- **Most accurate test:** If the diagnosis is uncertain, Wright and Giemsa stains show presence of large inclusion or molluscum bodies on histology.

KEY FACT

If you see giant molluscum contagiosum, think HIV or ↓ cellular immunity.

Treatment

- **Local destruction:** Curetting, cryotherapy, laser ablation, or applying cantharidin (a blistering agent) to the lesions.
- In children, lesions resolve spontaneously over months to years and are occasionally left untreated.

Verrucae (Warts)

Warts are caused by human papillomavirus (HPV) and can occur on skin, mucous membranes, and other epithelia. Although usually benign, some subtypes of HPV (especially 16 and 18) lead to squamous malignancies. Spread is by direct contact.

History/PE

- Common warts are most often seen on the hands, though they can occur anywhere.
- Classic genital warts (condyloma acuminatum, caused by HPV subtypes 6 and 11) are cauliflower-like papules or plaques appearing on the penis, vulva, or perianal region (Fig. 2.2-19).

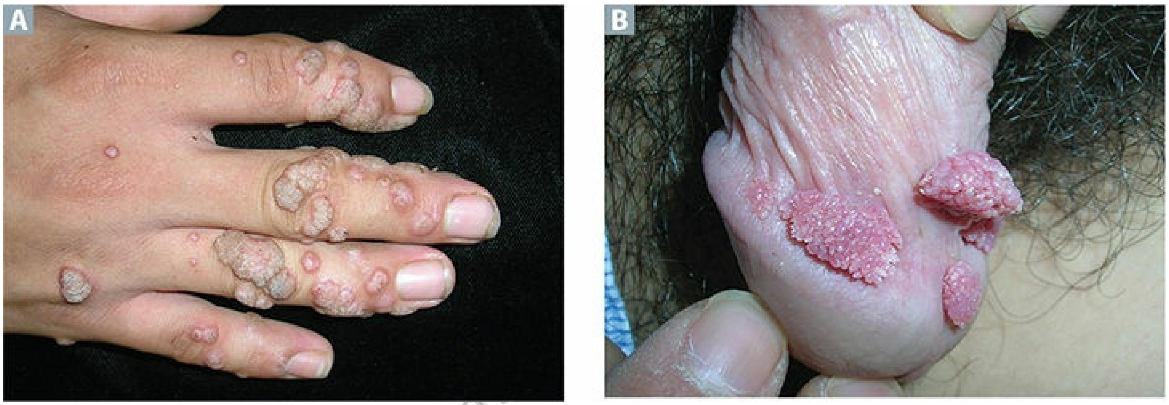


FIGURE 2.2-19. **Verrucae (warts) caused by HPV. (A)** Soft, tan-colored, cauliflower-like papules on hands. **(B)** Condyloma acuminatum on genitals. (Reproduced with permission from Dr. Richard Usatine.)

- Mothers with genital warts can transmit HPV to the infant by aspiration during delivery, causing respiratory papillomatosis. Presents as a weak cry, hoarseness, and stridor.

Diagnosis

- Characteristic exam findings and history are sufficient. Acetic acid turns lesions white and can be used to visualize mucosal lesions.
- **Most accurate test:** PCR of the lesion for HPV.

Treatment

Genital warts are treated surgically with cryotherapy, laser therapy, and excision. Chemical treatment includes podophyllin (contraindicated in pregnancy) and trichloroacetic acid, and immunologic treatment includes imiquimod (contraindicated in pregnancy). Cervical lesions are monitored for evidence of malignancy. Prevent via vaccination and barrier methods of contraception.

BACTERIAL INFECTIONS

Skin and soft tissue bacterial infections are a diverse group of diseases that manifest in different ways: red, inflamed papules and pustules centered around hair follicles are characteristic of folliculitis, while rapidly expanding, crepitant, dusky plaques suggest necrotizing fasciitis. Often, the clinical manifestation and treatment approach are dictated by the causative organism and the location of the infectious process within the layers of the skin and soft tissues. See Figure 2.2-20 for an illustration of the layers of the skin and associated depths of infection.

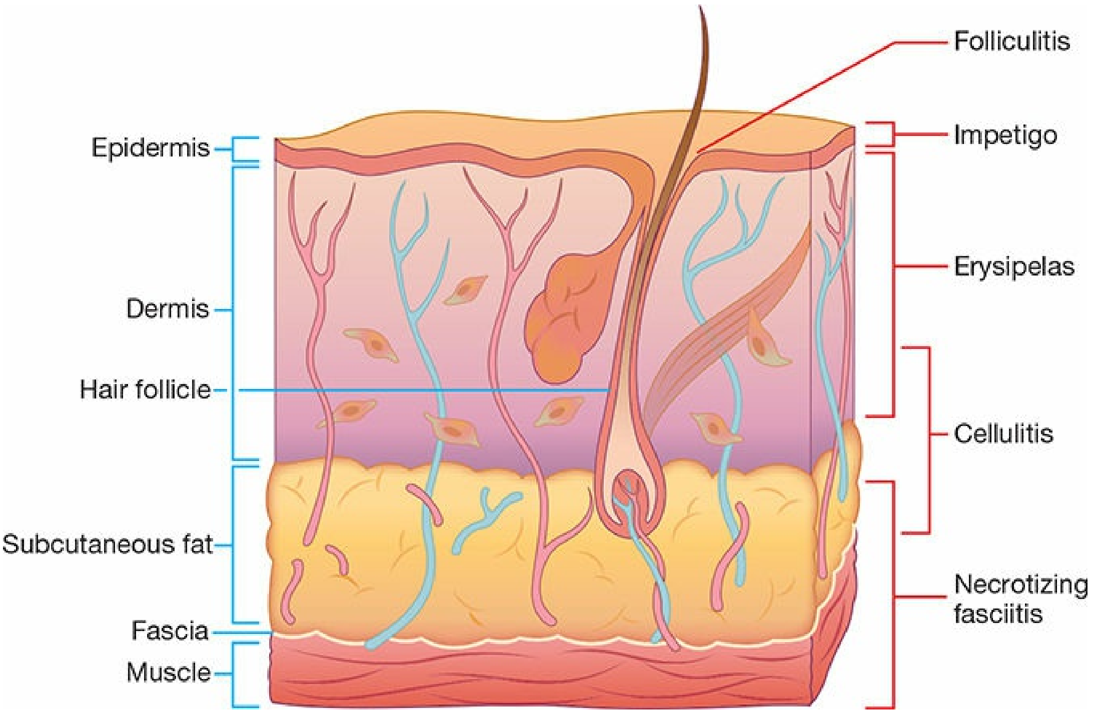

Epidermis
Dermis
Hair follicle
Subcutaneous fat
Fascia
Muscle
Folliculitis
Impetigo
Erysipelas
Cellulitis
Necrotizing fasciitis

FIGURE 2.2-20. **Skin layers *(blue)* and depths of infection *(red)*.** (Reproduced with permission from USMLE-Rx.com.)

Impetigo

Local infection of the epidermis that primarily occurs in children and is caused by both group A streptococcal and staphylococcal organisms. It is highly contagious and transmitted by direct contact.

History/PE

- **Nonbullous type:** Pustules and honey-colored crusts on an erythematous base, often on the face around the mouth, nose, or ears (Fig. 2.2-21). Commonly caused by *S aureus* or group A streptococci (GAS).

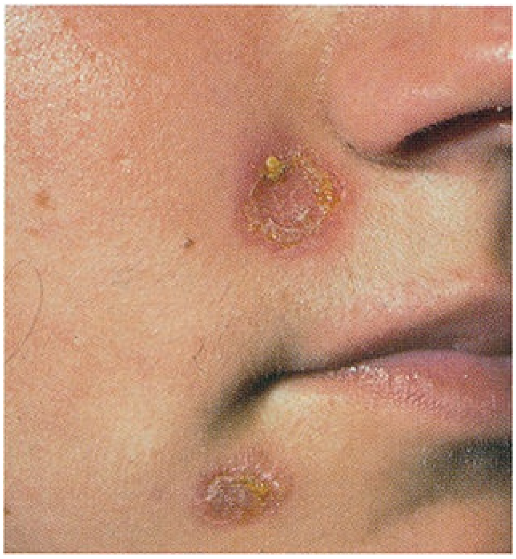


FIGURE 2.2-21. Impetigo. Dried pustules with a superficial golden-brown crust are most commonly found around the nose and mouth. (Reproduced with permission from Bondi EE. *Dermatology: Diagnosis and Therapy*. Stamford, CT: Appleton & Lange; 1991.)

- **Bullous type:** Characterized by flaccid bullae confined to the area of primary infection that form crusts when they rupture. Can involve the acral surfaces. Nikolsky sign is positive. Bullous impetigo is almost always caused by exfoliative toxin-producing strains of *S aureus* and can evolve into SSSS.
- **SSSS:** Systemic dissemination of exfoliative toxin destroys desmoglein-1 in the stratum granulosum of the skin. Presents as fever, generalized erythema, and widespread superficial blisters that do not form crusts when they rupture. Nikolsky is positive. Common in neonates, children, and adults with renal insufficiency.
- **Ecthyma:** Characterized by ulcerative lesions that extend into dermis. Appear as punched-out ulcers with yellow crusts.

Diagnosis

Clinical. Gram stain or culture to identify causative organism (not necessary to start treatment).

Treatment

Use antibiotics with antistaphylococcal activity based on severity and suspicion of methicillin-resistant *S aureus* (MRSA):

- **Mild localized disease:** Topical antibiotics (mupirocin) are sufficient.
- **Severe disease (non-MRSA) or ecthyma:** Oral cephalexin or dicloxacillin.
- **Severe disease (MRSA likely):** Oral trimethoprim-sulfamethoxazole, clindamycin, or doxycycline.
- **SSSS:** Nafcillin, vancomycin, and wound care.
- **Return to school**: The child may return to school 24 hours after the initiation of therapy.

Complications

- Acute poststreptococcal glomerulonephritis (PSGN)
- SSS

Cellulitis

A deeper skin infection involving dermis and subcutaneous tissue. Commonly caused by staphylococci or group A streptococci originating from damaged skin or a systemic source. Community-acquired MRSA is an increasingly common cause of purulent cellulitis. Risk factors include diabetes mellitus (DM), IV drug use, venous stasis, and immune compromise.

KEY FACT

Scarlet fever: “Sandpaper” rash or “sunburn with goose bumps” appearance; strawberry tongue. Caused by *S pyogenes.* Treat with penicillin.

KEY FACT

Salmonella typhi: Small pink papules on the trunk (“rose spots”) in groups of 10 to 20 plus fever and GI involvement. Treat with fluoroquinolones and third-generation cephalosporins. Consider cholecystectomy for chronic carrier state.

History/PE

- Presents with red, hot, swollen, tender skin. Fever and chills are common.
- Erysipelas is a type of cellulitis usually caused by GAS that is confined to the dermis and lymphatic tissue, creating a characteristically raised, indurated, well-demarcated, erythematous area of skin (Fig. 2.2-22).

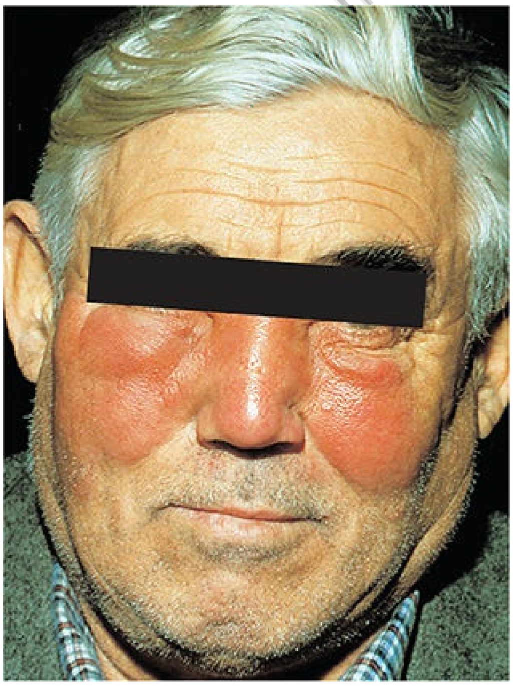


FIGURE 2.2-22. **Erysipelas of the face.** (Reproduced from Goldsmith LA et al. *Fitzpatrick’s Dermatology in General Medicine*, 8th ed. New York, NY: McGraw-Hill; 2012.)

Diagnosis

- Characteristic exam findings and history are sufficient. Wound and/or blood cultures may aid in diagnosis and help determine antibiotic sensitivities.
- Rule out abscess, osteomyelitis, and necrotizing fasciitis.

Treatment

- Topical antibiotics are ineffective due to depth of infection.
- Use 5 to 10 days of oral antibiotics. IV antibiotics are indicated if there is evidence of systemic toxicity, comorbid conditions, DM, extremes of age, or hand or orbital involvement.
- Choice of antibiotic is similar to that used to treat impetigo (empiric treatment of *S aureus* and GAS).

Necrotizing Fasciitis

Deep infection along a fascial plane causing severe pain followed by anesthesia and necrosis. Can be monomicrobial (GAS) or polymicrobial, usually caused by a mixed infection of anaerobic and aerobic bacteria that includes *S aureus*, *Escherichia coli*, and *Clostridium perfringens*. Ten percent of cases are caused by *S pyogenes*. A history of trauma or recent surgery to the affected area is sometimes present.

History/PE

- Systemic: Fever, chills, altered mental status (AMS).
- Acute onset of pain out of proportion to findings and swelling progressing to anesthesia at the site of trauma or surgery.
- An area of erythema quickly spreads over the course of hours to days. Margins move out into normal skin, and skin becomes dusky or purplish near the site of insult, ultimately leading to necrosis (Fig. 2.2-23).

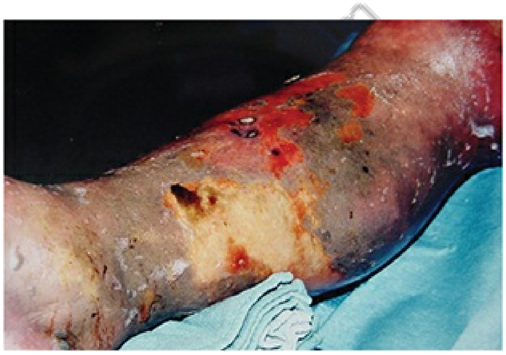


FIGURE 2.2-23. **Necrotizing fasciitis of the lower extremity.** Patient presented with hypotension due to late necrotizing fasciitis and myositis due to β-hemolytic streptococcal infection. (Reproduced with permission from Brunicardi FC et al. *Schwartz's Principles of Surgery*, 9th ed. New York, NY: McGraw-Hill; 2010.)

- If a necrotic area is open, gloved fingers can easily pass between two layers to reveal yellow-green necrotic fascia (infection spreads quickly in deep fascia).
- Important signs of tissue necrosis are gas production (crepitus on physical exam); a putrid, gray-colored discharge (colloquially named dishwater fluid); bullae; severe pain; lack of inflammatory signs; and intravascular volume loss.

Diagnosis

Strong suspicion of necrotizing fasciitis based on clinical exam and imaging (showing gas in soft tissue) requires immediate surgical exploration and debridement; tissue culture helps determine causative organisms.

KEY FACT

Fournier gangrene is a form of necrotizing fasciitis that is localized to the genital and perineal area.

KEY FACT

Pseudomonas aeruginosa infection leads to “hot tub folliculitis,” a pruritic, pustular folliculitis. Look for a history of exposure to wet, aquatic environments.

Treatment

- **Surgical emergency:** Early and aggressive surgical debridement is critical.
- In most cases, systemic broad-spectrum coverage is necessary. If *Streptococcus* is the principal organism involved, penicillin G is the drug of choice. Clindamycin is added to ↓ exotoxin production. For anaerobic coverage, give metronidazole or a third-generation cephalosporin.

Folliculitis

Inflammation and/or infection of a hair follicle. Typically caused by infection with *Staphylococcus, Streptococcus*, and gram ⊖ bacteria. Occasionally can be caused by yeast such as *Candida albicans* or *M furfur*. Can occur on any area with follicles.

Q 1

A 7-year-old girl presents to the physician with fever, sore throat, and a facial rash. Physical examination reveals an erythematous pharynx without exudates and a red, painful patch on the child’s cheek that the mother notes has been expanding. What is the appropriate therapy?

Q 2

A 42-year-old man is admitted to the hospital for cellulitis after injuring his leg while swimming. He is febrile and has a well-demarcated area of erythema on the anterior aspect of his right knee. Antibiotics are started. Six hours later, the patient is in excruciating pain. The erythema has spread circumferentially around the knee, and the anterior aspect of the knee now has a purplish hue. What is the next best step?

History/PE

- Presents as a tiny pustule at the opening of a hair follicle with a hair penetrating it. When the infection is deeper, a furuncle, or hair follicle abscess, develops. Furuncles may disseminate to adjacent follicles to form a carbuncle (Fig. 2.2-24).

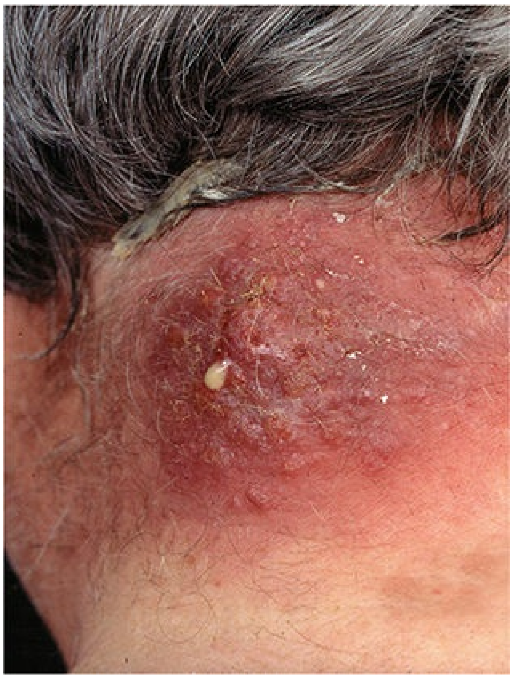


FIGURE 2.2-24. **Carbuncle due to methicillin-sensitive *S aureus*.** A very large, inflammatory plaque studded with pustules, draining pus, on the nape of the neck. Infection extends down to the fascia and has formed from a confluence of many furuncles. (Reproduced with permission from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology,* 7th ed. New York, NY, McGraw-Hill; 2013.)

- Patients with exposure to hot tubs, DM, or immunosuppression are at ↑ risk. Eosinophilic folliculitis can occur in AIDS patients, in whom the disease is intensely pruritic and resistant to therapy.

Diagnosis

Characteristic exam findings and history are sufficient. KOH prep or biopsy may be needed if fungus or eosinophilic folliculitis is suspected.

Treatment

Topical antibiotics (mupirocin) treat mild superficial disease. More severe disease is treated similarly to impetigo, with cephalexin or dicloxacillin orally, escalating to clindamycin or doxycycline if MRSA is suspected. Hot tub folliculitis due to *Pseudomonas* is self-limiting and does not usually require treatment—severe disease can be treated with ciprofloxacin.

Acne Vulgaris

A skin disease common among adolescents. The pathogenesis involves hormonal activation of sebaceous glands, the development of comedones (plugged pilosebaceous units), and involvement of *Cutibacterium acnes* (formerly *Propionibacterium)* in the follicle, causing inflammation. Acne lesions can be caused by medications (lithium, corticosteroids) or by topical occlusion (cosmetics). Commonly seen with congenital adrenal hyperplasia, polycystic ovarian syndrome (PCOS), and Cushing syndrome.

History/PE

- **There are three stages of acne lesions:**
  - **Comedonal:** Open ("blackheads") or closed ("whiteheads") comedones.
  - **Inflammatory:** The comedones rupture, creating inflammatory papules, pustules, nodules, and cysts.

  - **Scar:** May develop as inflammation heals. Picking at lesions exacerbates scarring.
- Acne develops at puberty and typically persists for several years. Male adolescents are more likely to have severe cystic acne than females due to greater androgen production.
- Women in their 20s can have a variant that flares cyclically with menstruation, with fewer comedones but more painful lesions on the chin.
- Drug-induced acne is a common adverse effect of glucocorticoid use. These lesions are monomorphic papules without comedones, nodules, or cysts and do not respond to standard acne therapy. However, they usually resolve with discontinuation of the steroids.
- Acne mechanica occurs due to pressure or friction. Constant mechanical pressure damages pilosebaceous units causing obstruction and acne formation. Treat by eliminating the source of pressure. Can be caused by crutches, bra straps, and heavy backpacks.

KEY FACT

Ironically, erythromycin does not cause erythema with sun exposure. It is tetracyclines (ie, doxycycline) that can cause photosensitivity!

1 A

This child has erysipelas, a rash commonly caused by a GAS infection. It can present as a small red patch on the cheek or extremities that turns into a painful, shiny red plaque. Patients often have a history of chronic cutaneous ulcers, lymphedema, or pharyngitis. Treat with penicillin.

2 A

Emergent surgical consult for debridement given the clinical suspicion for necrotizing fasciitis, a surgical emergency.

Diagnosis

Characteristic exam findings and history are sufficient.

Treatment

- **Mild to moderate acne:** Topical retinoids are the most effective topical agent for comedonal acne. Topical benzoyl peroxide kills *C acnes*. Consider adding a topical antibiotic (clindamycin, erythromycin) if response to other topicals is inadequate.
- **Moderate to severe acne:** In addition to topical treatment as noted earlier, add oral antibiotics such as doxycycline or minocycline. When acne is severe and all treatments are failing, oral retinoids (isotretinoin) are the most effective treatment. All other acne medications are stopped.
  - Isotretinoin is a teratogen and elevates LFTs. Patients require periodic blood tests to check liver function, cholesterol, and triglycerides. Given the teratogenicity of isotretinoin, female patients must be on two forms of contraception (ie, barrier and hormonal) and are monitored with baseline and serial pregnancy tests.

Pilonidal Cysts

Abscesses in the sacrococcygeal region. Thought to be a foreign body reaction to entrapped hair. Most common in young men with excessive body hair.

History/PE

Presents as an abscess at the superior gluteal cleft (Fig. 2.2-25) that can be tender, fluctuant, and warm—sometimes associated with purulent drainage or cellulitis. Systemic symptoms are uncommon, but cysts can develop into perianal fistulas.

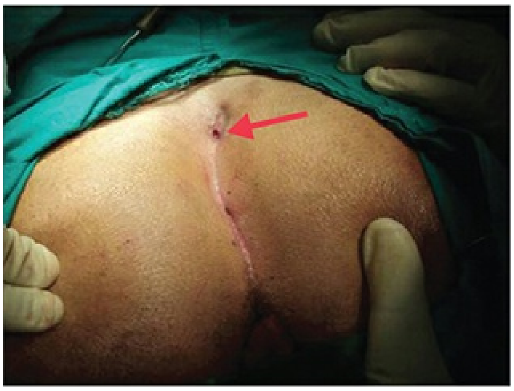


FIGURE 2.2-25. **Pilonidal cyst.** Note the characteristic location in the superior gluteal cleft. May have purulent dis-charge, surrounding erythema, or a tuft of hair. (Reproduced with permission from Awad MM, Elbaset AA, Ebraheem S, Tantawy E, Elhafez MA, Elsayed AM. A scoring system as a method to evaluate pilonidal sinus disease to make an easy decision for its management. *Indian J Plast Surg.* 2009;42(1):43-48. doi:10.4103/0970-0358.53011.)

Diagnosis

Characteristic exam findings and history are sufficient.

KEY FACT

General progression of acne treatment based on severity: topical benzoyl peroxide, retinoid, or antibiotic → oral antibiotic → oral isotretinoin

KEY FACT

Antibiotics are not needed for pilonidal cysts unless cellulitis is present; if antibiotics are prescribed, both aerobic and anaerobic coverage is required.

Treatment

- Treatment is with incision and drainage of the abscess followed by sterile packing of the wound.
- Excision of sinus tract if present.
- Good local hygiene and shaving of the sacrococcygeal skin can help prevent recurrence.

Leprosy

Disease of skin and peripheral nerves, found in the Southwest United States and developing countries. Caused by acid-fast bacterium *Mycobacterium leprae* and causes chronic granuloma formation.

History/PE

Patients present with hypopigmented, hypoesthetic skin lesions, nerve thickening, and palsies of peripheral nerves. Clinical manifestations depend on type of leprosy.

- Tuberculoid: One to two localized hypopigmented anesthetic plaques
- Lepromatous: Many plaques or nodules, leonine facies, hair loss (particularly eyebrows and lashes), septal perforation

Diagnosis

- Skin scraping
- Punch biopsy
- Lepromin test

Treatment

- Treat tuberculoid leprosy with dapsone and rifampin.
- Add clofazimine for lepromatous or multibacillary leprosy.

Q

A 17-year-old female presents to the dermatologist for severe cystic acne that has been refractory to both topical and systemic antibiotics. She inquires about isotretinoin. Given this drug's potentially hazardous adverse effects, what laboratory tests would be performed monthly if this patient were to be placed on isotretinoin?

FUNGAL INFECTIONS

Tinea Versicolor

Caused by *Malassezia* species, a yeast that is part of normal skin flora. Humid and sweaty conditions, as well as oily skin, can make the organism pathogenic. Cushing syndrome and immunosuppression are also risk factors.

History/PE

- Presents with small scaly patches of varying color on the chest or back (Fig. 2.2-26A).

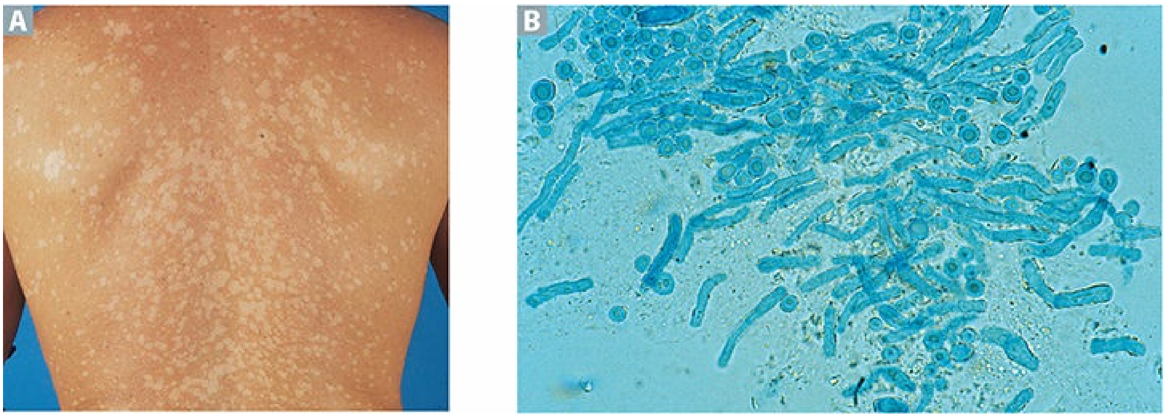


FIGURE 2.2-26. **Tinea versicolor. (A)** Note the discrete, hypopigmented patches extensively involving the patient's back. Tinea versicolor may also present as hyperpigmented macules or patches in some individuals. **(B)** KOH preparation shows the characteristic "spaghetti and meatballs" pattern of hyphae and spores. (A reproduced with permission from Tintinalli JE et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide,* 7th ed. New York, NY: McGraw-Hill; 2011. B reproduced with

permission from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th ed. New York, NY: McGraw-Hill; 2008.)

- Patches can be hypopigmented (alba) as a result of interference with melanin production or hyperpigmented/pink (rubra) due to inflammation.
- Often discovered after sun exposure when lesions fail to tan and stand out.

Diagnosis

- Characteristic exam findings and history are usually sufficient, but confirmatory testing is useful to differentiate from other dermatologic disorders with similar findings.
- **Best initial test:** KOH preparation of the scale revealing "spaghetti and meatballs" pattern of hyphae and spores (see Fig. 2.2-26B).

Treatment

Treat lesions with topical ketoconazole or selenium sulfide.

Candidiasis

Yeast infection or thrush, candidiasis can be caused by any *Candida* species but is most commonly caused by *C albicans*. In immunocompetent patients, it typically presents as eroded erythematous papules and plaques in intertriginous, moist areas such as the groin, skinfolds, axillae, vagina, and below the breasts. Oral thrush is common in infancy, but in adults it is often a sign of a weakened immune system.

History/PE

- Patients often have a history of antibiotic or steroid use, DM, or immunocompromise.

A

The laboratory tests to be performed monthly for a female patient taking isotretinoin for severe cystic acne would be serum or urine β-human chorionic gonadotrophin to rule out pregnancy, liver function tests (LFTs), cholesterol, and triglycerides.

- **Oropharyngeal candidiasis (thrush):** Presents with painless white plaques on intraoral mucosal surfaces that can be easily scraped off to reveal erosions.
- **Candidiasis of the skin:** Presents as markedly erythematous papules and plaques with occasional erosions and smaller satellite lesions (Fig. 2.2-27) seen nearby, often in skinfolds. In infants, infection is often seen in the diaper area and along the inguinal folds.

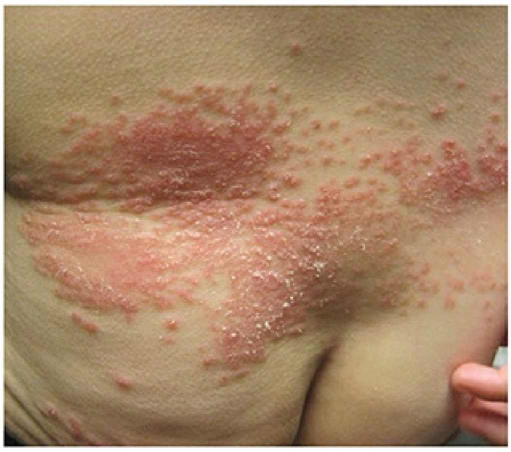


FIGURE 2.2-27. **Cutaneous candidiasis with satellite lesions.** (Reproduced with permission from Goldsmith LA et al. *Fitzpatrick's Dermatology in General Medicine*, 8th ed. New York, NY: McGraw-Hill; 2012.)

- **Vulvovaginal candidiasis:** Vaginal burning, dysuria, pruritis, white "cottage-cheese" discharge.
- **Candida esophagitis:** Odynophagia in a patient with hematologic malignancy or AIDS.

Diagnosis

- Characteristic exam findings and history are sufficient.
- **Best initial test:** KOH preparation of a scraping of the affected area. KOH dissolves the skin cells but leaves the *Candida* untouched such that Candida spores and pseudohyphae become visible.
- **Most accurate test:** Blood culture.
- Endoscopy if esophageal involvement, antigen testing, tissue biopsy.

Treatment

- **Oral candidiasis:** Oral fluconazole tablets; nystatin swish and swallow, clotrimazole troches.
- **Esophageal candidiasis:** Systemic fluconazole, echinocandins, amphotericin B.
- **Superficial (skin) candidiasis:** Topical antifungals; keep skin clean and dry.
- **Vulvovaginal candidiasis:** Topical antifungal, single dose of oral fluconazole.
- **Diaper rash:** Topical nystatin.

Dermatophyte Infections

Dermatophytes are found in tissues with keratin (skin, nails, and hair). Causative organisms include *Trichophyton* (most common), *Microsporum*, and *Epidermophyton* species. Risk factors include DM, ↓ peripheral circulation, immune compromise, and chronic maceration of skin (from athletic activities). A common cause of recurrent infections is autoinoculation from a tinea infection on another site of the body.

History/PE

Varies according to subtype:

- **Tinea corporis (ringworm):** Scaly, pruritic eruption with a well-demarcated, irregular border, often with central clearing (Fig. 2.2-28). Can be seen in immunocompromised patients or in children following contact with infected pets. The term *ringworm* is a misnomer due to the characteristic appearance of the lesion—it is caused by a fungus, not a worm or parasitic infection.

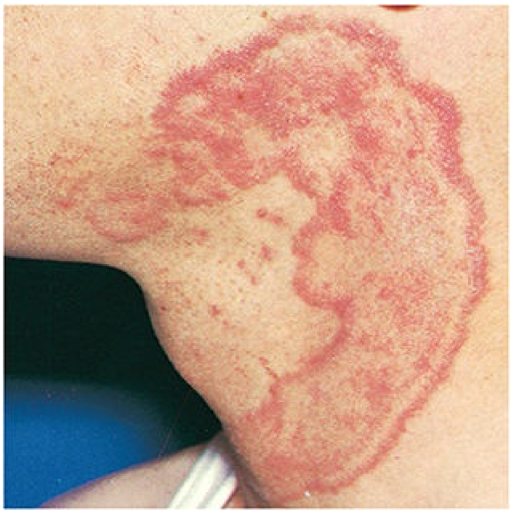


FIGURE 2.2-28. **Tinea corporis.** Note the ringworm rash with a scaly, erythematous, distinct border and central clearing. (Reproduced with permission from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th ed. New York, NY: McGraw-Hill; 2008.)

- **Tinea pedis/manuum** (Fig. 2.2-29A): Presents as chronic interdigital scaling with erosions between the toes (athlete's foot) or as a thickened, scaly skin on the soles (moccasin distribution). In addition, involvement of one hand is typical in the "one hand two feet syndrome."

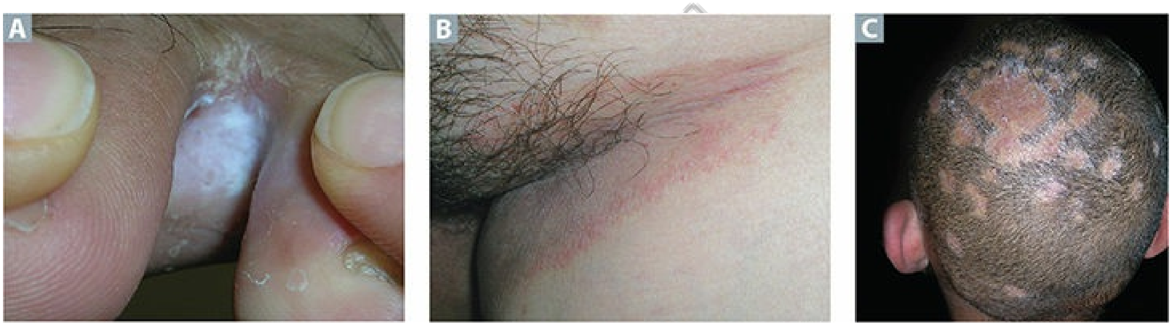


FIGURE 2.2-29. **Cutaneous mycoses. (A)** Tinea pedis; **(B)** Tinea cruris; **(C)** Tinea capitis. (Reproduced with permission from Dr. Richard Usatine.)

- **Tinea cruris (jock itch)** (Fig. 2.2-29B): A fungal infection of the groin that is usually associated with tinea pedis. Pruritic plaque without central clearing, typically sparing the scrotum.
- **Tinea capitis** (Fig. 2.2-29C): A fungal scalp infection causing scaling and hair loss with scarring. A large inflammatory boggy mass caused by tinea capitis is called a kerion.
- **Tinea unguium (onychomycosis):** A fungal nail infection causing brittle, discolored nails.

Diagnosis

- Clinical
- **Best initial test:** KOH skin scraping showing hyphae
- **Most accurate test:** Fungal culture
- Wood's lamp exam for *Microsporum* species

Treatment

Start with topical antifungals; escalate to oral griseofulvin or terbinafine if infection is widespread or unresponsive to topicals. Oral antifungals are indicated for nail involvement and tinea capitis (to penetrate into hair follicles); consider oral treatment for immunocompromised patients.

Sporotrichosis

Infection caused by *Sporothrix schenckii*, a fungus found in plant matter. Often called "rose-gardener disease." Acquired by direct contact, which causes a papule that drains odorless fluid. Additional lesions form over time along lines of lymphatic drainage, although lymphadenopathy is absent. Treat with itraconazole.

PARASITIC INFECTIONS

Lice

Lice live off blood and on specific parts of the body, depending on their species (head lice, body lice, pubic lice). They are spread through body contact or by the sharing of bedclothes and other garments or hair accessories. Lice secrete local toxins that lead to pruritus.

History/PE

- Patients with lice often experience severe pruritus, and secondary bacterial infection of the excoriations is a risk. Classroom breakouts of head lice are common.
- Body lice are seen in persons with inadequate hygiene or in those with crowded living conditions. Pubic lice (called "crabs" because of their squat, crablike body shape) contain anticoagulant in their saliva, so their bites often become ecchymotic.

Diagnosis

Lice and their eggs (nits) can be seen on hairs or in clothes with the naked eye. Microscopy can reveal the arthropods, their eggs, and their droppings.

Treatment

- **Head lice:** Treat with topical permethrin, pyrethrin, benzyl alcohol, and mechanical removal.
- **Body lice:** Wash body, clothes, and bedding thoroughly. Rarely, topical permethrin is needed.
- **Pubic lice:** Treat with the same medications as for head lice.

Scabies

Caused by *Sarcoptes scabiei*. The burrowing of this arthropod into the epidermis leads to pruritus that ↑ in intensity once an allergy to the mite or its products develops. Secondary bacterial infections due to scratching are common. Scabies mites are spread through close contact.

History/PE

- Patients present with intense pruritus, especially at night and after hot showers, and erythematous papules with linear tracts, representing the burrows of the mite (Fig. 2.2-30A).

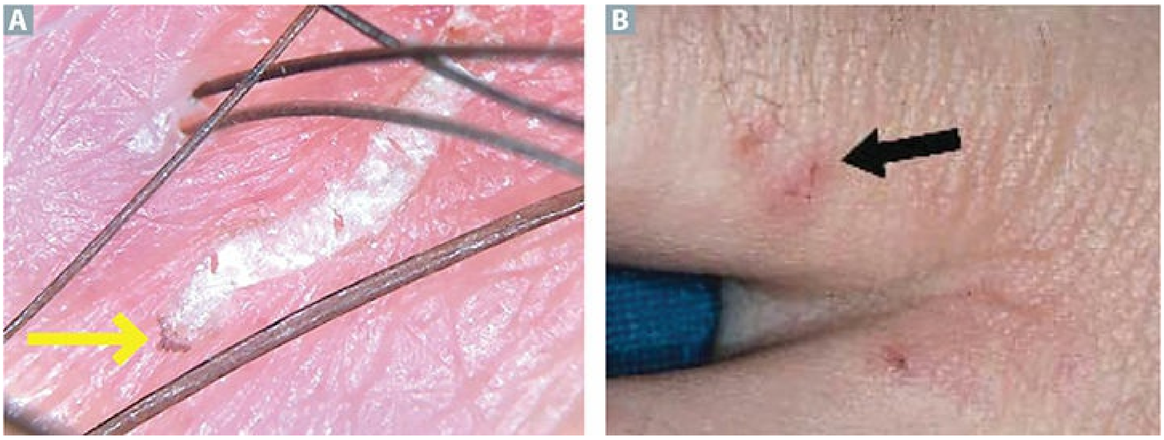


FIGURE 2.2-30. **Scabies. (A)** Linear tracts made as the mite burrows into the skin *(yellow arrow)*. **(B)** Erythema-tous papules in interdigital web spaces *(black arrow)*. (A reproduced with permission from Micali G et al. Scabies: Advances in noninvasive diagnosis. *PloS Negl Trop Dis*. Published 16 Jun. 2016;10.(6):e0004691. doi:10.1371/journal.pntd.0004691. B reproduced with permission from Siegfried EC, Hebert AA. Diagnosis of atopic dermatitis: Mimics, overlaps, and complications. *J Clin Med.* 2015;4[5]:884-917. doi:10.3390/jcm4050884)

- The most commonly affected sites are the skinfolds of the hands (often includes the interdigital finger webs), axillae, genitals, and flexor surfaces of the wrists (see Fig. 2.2-30B).
- Crusted scabies is severe, diffuse skin involvement with crusts and scales seen in the immunocompromised (eg, HIV).

Diagnosis

A history of pruritus in several family members is suggestive. The mite may be identifiable by scraping an intact tunnel and looking under the microscope for the arthropods, their eggs, and their droppings.

KEY FACT

Lice can be seen with the naked eye. Scabies mites are too small and can only be identified with a microscope/dermatoscope.

Treatment

- Patients should be treated with 5% permethrin from the neck down (head to toe for infants) for at least two treatments separated by 1 week, and their close contacts should be treated as well. Oral ivermectin is also effective.
- Treatment for crusted scabies: Oral ivermectin in combination with topical permethrin.
- Pruritus can persist up to 2 weeks after treatment.
- Clothes and bedding should be thoroughly washed.

Bed Bugs

Painless erythematous papules on exposed skin due to bites from *Cimex lectularius* at night. Mild pruritus, which is worse at night and in the morning. Lesions seen in a linear “breakfast, lunch, and dinner” pattern. Transmitted by contact with infested beddings and furniture. Treat pruritis with topical steroids and antihistamines; use insecticides or heat to remove infestation.

Cutaneous Larva Migrans

Erythematous, serpentine, migratory rash marked by pruritic maculopapular lesion at the site of larval entry due to infection with hookworm larvae, commonly acquired by walking barefoot on grass or sand. Treat with ivermectin.

ISCHEMIC SKIN DISORDERS

DECUBITUS ULCERS

Result from ischemic necrosis following continuous pressure on an area of skin that restricts microcirculation (Fig. 2.2-31).

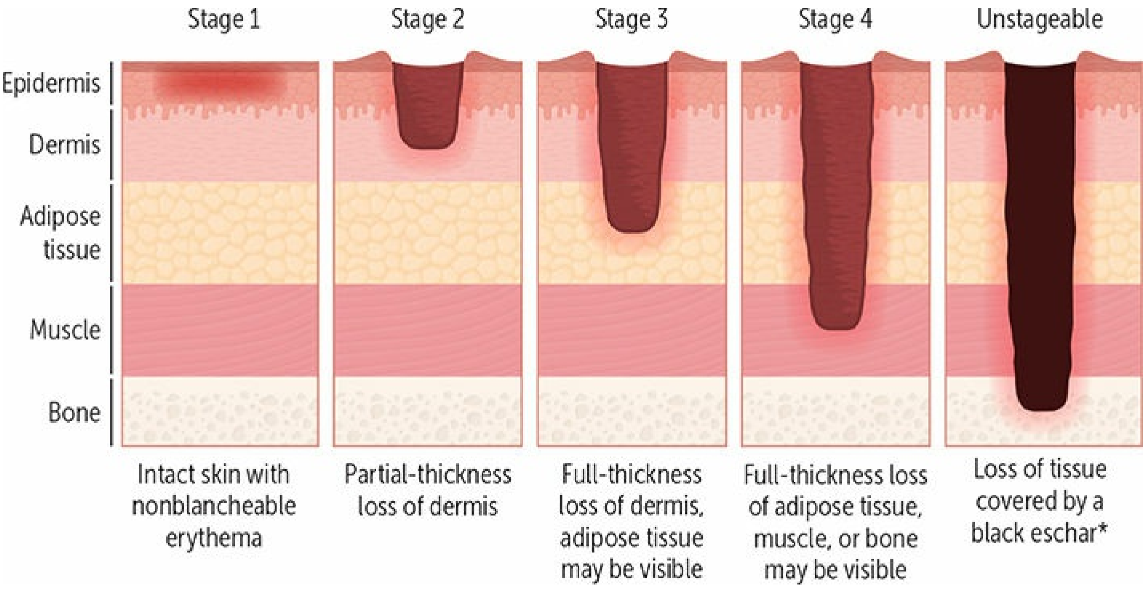

Stage 1
Stage 2
Stage 3
Stage 4
Unstageable
Epidermis
Dermis
Adipose tissue
Muscle
Bone
Intact skin with nonblancheable erythema
Partial-thickness loss of dermis
Full-thickness loss of dermis, adipose tissue may be visible
Full-thickness loss of adipose tissue, muscle, or bone may be visible
Loss of tissue covered by a black eschar*

FIGURE 2.2-31. **Depth of skin ulcers.** Stage 1 involves intact skin with nonblanchable erythema. Stage 2 involves partial-thickness loss of dermis; however, deeper structures are intact. Stage 3 involves full-thickness loss of epidermis and subcutaneous fascia; however, muscle and bone are not exposed. Stage 4 involves full-thickness tissue loss with exposed underlying structures such as muscle or bone. Unstageable ulcers are covered with black eschar, making it difficult to determine depth of injury. (Reproduced with permission from USMLE-Rx.com.)

History/PE

Ulcers are commonly seen in bedridden patients who lie in the same spot for too long. An underlying bony prominence or lack of fat ↑ the likelihood of ulcer formation (sacrum, heels). Patients with prolonged intensive care unit (ICU) stays or lacking mobility or cutaneous sensation are also at ↑ risk. Incontinence of urine or stool may macerate the skin, facilitating ulceration.

Diagnosis

Characteristic exam findings and history are sufficient. Occasionally, a biopsy can be performed on a nonhealing ulcer to rule out cutaneous squamous cell carcinoma, infection, and/or pyoderma gangrenosum. Bone biopsy to diagnose osteomyelitis if bony exposure.

Treatment

- **Prevention is key:** Routinely reposition bedridden patients (at least once every 2 hours); special beds can distribute pressure. Nutritional optimization to promote wound healing.
- If an ulcer develops, low-grade lesions can be treated with routine wound care, including hydrocolloid dressings. High-grade lesions require surgical debridement.

GANGRENE

Necrosis of body tissue. There are three subtypes as follows:

- **Dry gangrene:** Due to insufficient blood flow to tissue, typically from atherosclerosis.
- **Wet gangrene:** Involves bacterial infection, usually with skin flora.
- **Gas gangrene:** Due to *C perfringens* infection.

History/PE

- **Dry gangrene:** Early signs are a dull ache, cold, and pallor of the flesh. As necrosis sets in, the tissue (toes, fingers) becomes bluish-black, dry, and shriveled. Diabetes, vasculopathy, and smoking are risk factors.
- **Wet gangrene:** The tissue appears bruised, swollen, or blistered with pus.
- **Gas gangrene:** Occurs at sites of large trauma/surgery compromising blood flow to a region, bringing about an anaerobic environment. Bacteria rapidly destroy tissue, producing gas that separates healthy tissue and exposes it to infection. Associated with dirty wounds contaminated with dirt or bowel/fecal matter. IV drug use is a risk factor. Presents with swelling and pale or dark-red skin around the injury. A medical emergency.

Diagnosis

Characteristic exam findings and history are sufficient. Air in soft tissue on x-ray is very suggestive of necrosis (Fig. 2.2-32).

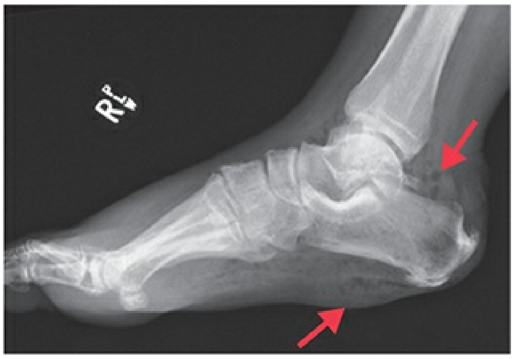


FIGURE 2.2-32. **Gas gangrene.** X-ray of the foot showing gas tracking through soft tissues, most clearly seen overlying the calcaneus. (Reproduced with permission from Tintinalli JE et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide,* 7th ed. New York, NY: McGraw-Hill; 2011.)

Treatment

- Emergency surgical debridement, with amputation if necessary, is the mainstay of treatment. Antibiotics alone do not suffice by virtue of inadequate blood flow, but they should be given as an adjuvant to surgery.
- Hyperbaric oxygen (toxic to the anaerobic *C perfringens*) can be used after debridement to help with treatment.

MISCELLANEOUS SKIN DISORDERS

STASIS DERMATITIS

Lower extremity dermatitis due to venous hypertension forcing blood from the deep to the superficial venous system. Venous hypertension is often a result of venous valve incompetence or flow obstruction. It commonly involves the medial ankle in patients with deep vein thrombosis (DVT) history, chronic edema, and long periods of standing. If untreated, the area can become inflamed, exudative, and hyperpigmented from hemosiderin deposition (Fig. 2.2-33). Stasis ulcers may develop. Treat early with leg elevation, compression stockings, emollients, and topical steroids.

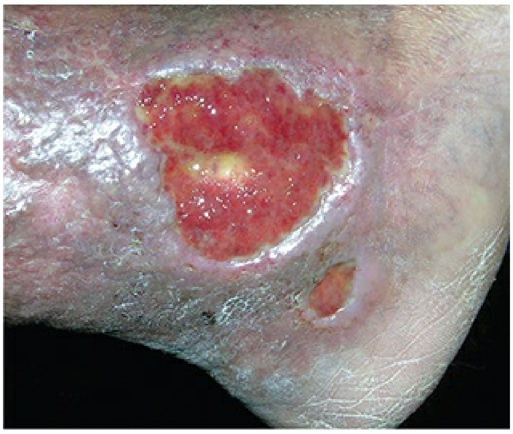


FIGURE 2.2-33. **Stasis dermatitis.** Venous ulceration with stasis dermatitis, edema, and varicosities. (Reproduced with permission from Dr. Richard Usatine.)

ACANTHOSIS NIGRICANS

- A condition in which the skin in the intertriginous zones (neck folds, genitals, axillae) becomes hyperkeratotic and hyperpigmented with a velvety appearance (Fig. 2.2-34).

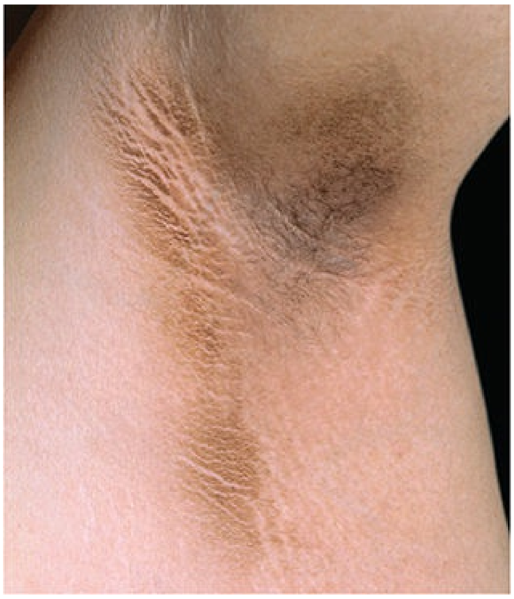


FIGURE 2.2-34. **Acanthosis nigricans.** Velvety, dark-brown epidermal thickening of the armpit

is seen with prominent skinfold and feathered edges. (Reproduced with permission from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology.* 7th ed. New York, NY: McGraw-Hill; 2013.)

- Associated with DM (insulin resistance), Cushing disease, PCOS, and obesity. May also be a paraneoplastic sign of underlying adenocarcinoma (usually GI).
- **Treatment:** Typically not treated. The physician can encourage weight loss and treat the underlying endocrinopathy.

LICHEN PLANUS

A self-limited, recurrent, or chronic inflammatory disease affecting the skin, oral mucosa, and genitalia. Lesions classically described using the **6 *P*s** (**P**lanar, **P**urple, **P**olygonal, **P**ruritic, **P**apules, and **P**laques). It may be induced by drugs (thiazides, quinines, β-blockers) and is associated with HCV infection.

History/PE

Presents with violaceous, flat-topped, polygonal papules (Fig. 2.2-35). Wickham striae (lacy white lines) may be present on the lesion. Lesions may demonstrate prominent Koebner phenomena (lesions that appear at the site of trauma).

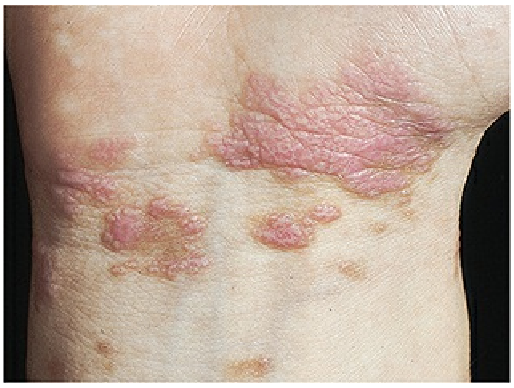


FIGURE 2.2-35. **Lichen planus.** Flat-topped, polygonal, sharply defined papules of violaceous color are grouped and confluent. The surface is shiny and reveals fine white lines (Wickham striae). (Reproduced with permission from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine.* 7th ed. New York, NY: McGraw-Hill; 2008.)

Treatment

Mild cases are treated with topical corticosteroids. For severe disease, systemic corticosteroids and phototherapy may be used.

ROSACEA

A chronic disorder of pilosebaceous units of which the etiology is unclear.

Diagnosis

Presentation can vary depending on the subtype as follows:

- **Erythematotelangiectatic rosacea:** Presents with central facial erythema with telangiectasias.
- **Papulopustular rosacea:** Develops papules and pustules.
- **Phymatous rosacea:** Connective tissue overgrowth on the chin, forehead, and other areas

of the face. May lead to severe overgrowth of nasal connective tissue known as rhinophyma (Fig. 2.2-36).

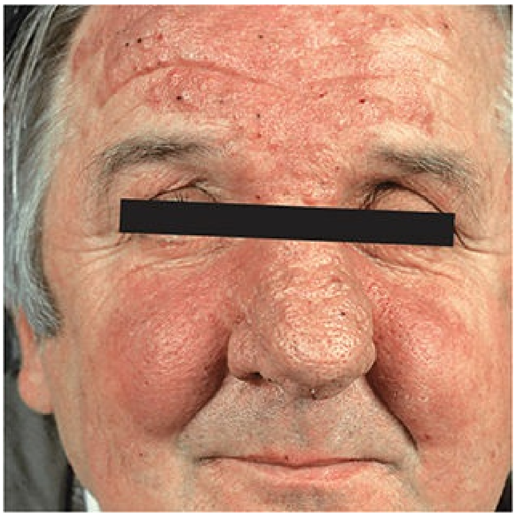


FIGURE 2.2-36. **Rhinophyma.** (Reproduced with permission from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*. 7th ed. New York, NY: McGraw-Hill; 2008.)

- **Ocular rosacea:** Can predispose to blepharitis, stye, and chalazion formation.

History/PE

- Patients are middle-aged with fair skin and often have an abnormal flushing response to hot drinks, spicy foods, alcohol, and sun. There is a female predominance.
- Often referred to as "adult acne" because it can present similarly to acne but involves an older age group.

Treatment

- Behavioral: sunlight and alcohol avoidance, skin hygiene, and emollient use
- Erythematotelangiectatic rosacea: topical brimonidine or laser therapy
- Papulopustular rosacea: topical metronidazole
- Phymatous rosacea: oral isotretinoin or laser therapy
- Severe/ocular rosacea: oral doxycycline

PITYRIASIS ROSEA

An acute dermatitis of unknown etiology that has been hypothesized to represent a reaction to a viral infection with HHV-7.

History/PE

- Initial lesion is classically a herald patch that is erythematous with a peripheral scale.
- Days to weeks later, a secondary eruption appears: multiple scaling papules and plaques with a fine "cigarette paper" scale (Fig. 2.2-37). Papules are arranged along skin lines, giving a classic "Christmas tree" pattern on the patient's back.

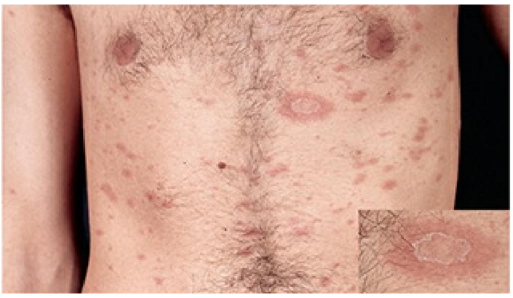


FIGURE 2.2-37. **Pityriasis rosea.** The round to oval erythematous plaques are often covered with a fine white scale (“cigarette paper”) and are often found on the trunk and proximal extremities. Plaques are often preceded by a larger herald patch *(inset).* (Reproduced with permission from Tintinalli JE et al. *Tintinalli’s Emergency Medicine: A Comprehensive Study Guide.* 7th ed. New York, NY: McGraw-Hill; 2011.)

KEY FACT

Pityriasis rosea spares palms and soles, whereas secondary syphilis does not.

Diagnosis

Diagnosis is clinical. Confirm with KOH exam to rule out fungus (the herald patch may be mistaken for tinea corporis). Consider testing for secondary syphilis, which can present similarly.

Treatment

Rash heals in 6 to 8 weeks without any treatment. Supportive therapy to manage symptoms includes emollients and antihistamines.

VITILIGO

Autoimmune destruction of melanocytes leading to well-demarcated areas of depigmentation. Frequently associated with other autoimmune diseases, such as hypothyroidism and type I DM.

- **History/PE:** Sharply demarcated, depigmented macules or patches on otherwise normal skin, often on the hands, face, or genitalia (Fig. 2.2-38). Vitiligo can present at any age and vary from small areas of involvement with or without progression to large areas of depigmentation.

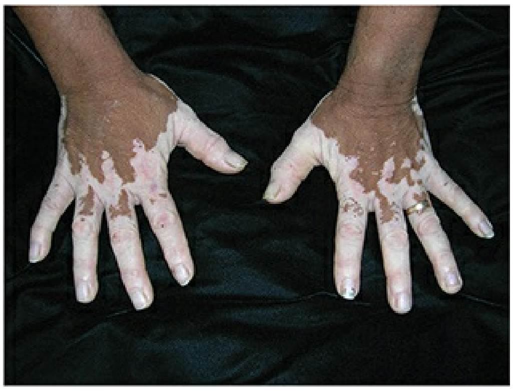


FIGURE 2.2-38. **Vitiligo of the hands.** Areas of sharply demarcated depigmentation. (Reproduced

with permission from Dr. Richard Usatine.)

- **Diagnosis:** Often clinical. Many patients have serologic markers of autoimmune disease (eg, antithyroid antibodies, type 1 DM, pernicious anemia) and occasionally present with these diseases. Histologic examination demonstrates the absence of melanocytes and melanin pigment. Examination of skin under Wood's lamp may be helpful for diagnosis.
- **Treatment:** For patients with rapidly progressive vitiligo, oral glucocorticoids can be used to prevent further spread of lesions. Topical corticosteroids, tacrolimus ointment, JAK inhibitors, UV, and laser therapy can be used in stable vitiligo. Sunscreen prevents burns. Cover-up makeup can help with cosmetic concerns.

EYELID LESIONS

- **Xanthelasma:** Soft yellow plaques seen on the medial aspects of the eyelids bilaterally (Fig. 2.2-39), associated with hyperlipidemia and primary biliary cirrhosis. Serum total cholesterol is often normal. Treatment is not necessary.

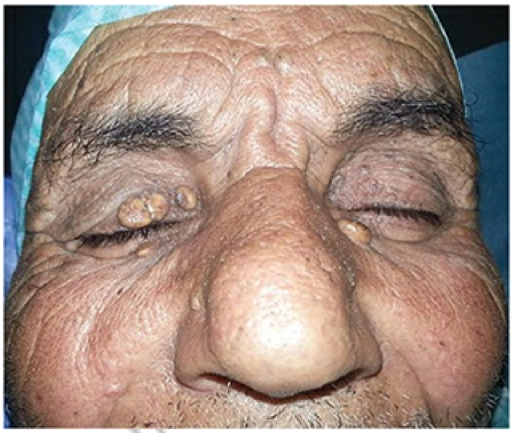


FIGURE 2.2-39. **Xanthelasma.** (Reproduced with permission from Elgazi T & Zouheir H. Xanthelasma. *Pan Afr Med J*. 2016;25:41. doi: 10.11604/pamj.2016.25.41.10510.)

- **Hordeolum:** Painful acute eyelid gland infection (stye), usually due to *S aureus* and located on the edge of the lid. Most resolve spontaneously, but warm, moist compresses may help.
- **Chalazion:** Chronic inflammatory painless cyst due to a blocked eyelid gland. Hordeolum can become a chalazion after the infection resolves.

EPIDERMAL INCLUSION CYSTS

- Dome-shaped, firm or freely movable cyst often surrounding a hair follicle (Fig. 2.2-40). Erythema, mild tenderness, and cheeselike discharge may be seen.

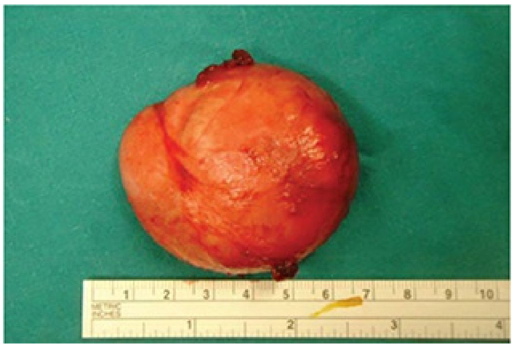


FIGURE 2.2-40. **Specimen of an epidermal inclusion cyst, with intact capsule.** The cyst is filled with keratin cells. (Reproduced with permission from Tsirevelou et al. Epidermoid cyst of the floor of the mouth: two case reports. *Cases J.* 2009;2:9360. doi: 10.1186/1757-1626-2-9360).

- Does not dimple when pinched (in contrast with dermatofibroma).
- Usually resolves spontaneously, but can recur; thus excision of large cysts is preferred.

DERMATOFIBROMA

- Dome-shaped, firm, brown-pink, nontender nodule often <1 cm in diameter resulting from fibroblast proliferation (Fig. 2.2-41).

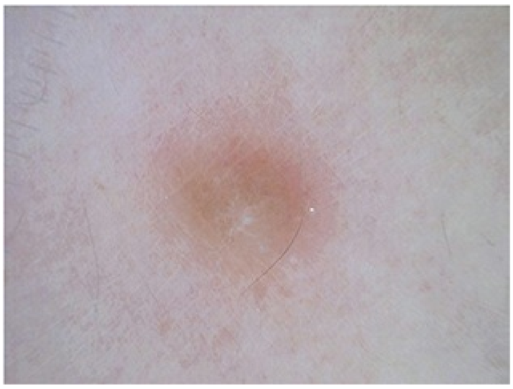


FIGURE 2.2-41. **Dermatofibroma.** Dome-shaped, brown-pink nodule that dimples when pinched. A benign lesion that can be excised for cosmetic reasons. (Reproduced with permission from Diluvio L, Torti C, Terrinoni A, et al. Dermoscopy as an adjuvant tool for detecting skin leiomyomas in patient with uterine fibroids and cerebral cavernomas. *BMC Dermatol.* 2014;14:7. doi:10.1186/1471-5945-14-7.)

- Dimples when pinched (dimple or buttonhole sign).
- Benign. Treatment with excision for cosmetic reasons.

HIDRADENITIS SUPPURATIVA

- Chronic inflammation of folliculopilosebaceous units causing inflamed, painful nodules that may progress to form sinus tracts and scars that secrete a malodorous discharge (Fig. 2.2-42). It is more common in people with family history, Black race, smoking history, diabetes, or obesity.

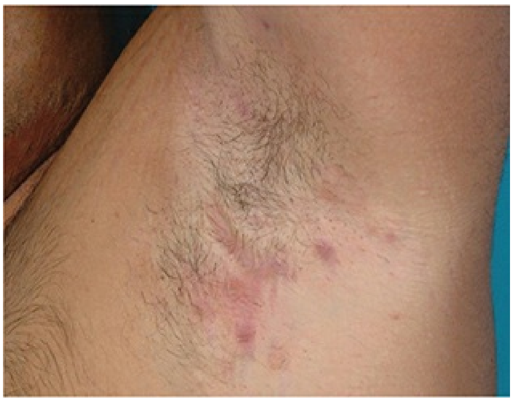


FIGURE 2.2-42. **Hidradenitis suppurativa.** Draining sinus tracts present in the axilla. Associated infection and cellulitis are common. (Reproduced with permission from Alharbi Z, Kauczok J, Pallua N. A review of wide surgical excision of hidradenitis suppurativa. *BMC Dermatol.* 2012;12:9.)

- Common in intertriginous areas (axilla, groin) and often has a chronic relapsing course.
- **Diagnosis:** Clinical. No biopsy needed.
- **Treatment:** Oral antibiotics (topical clindamycin is often first line), drainage, wound care, or surgical excision and skin grafting of affected areas. Could result in relapsing course despite medical and surgical management. Weight loss and smoking cessation are recommended.

ICHTHYOSIS VULGARIS

- Disorder of diffuse, dry dermal scaling that resembles fish scales (ichthyosis means "fishlike" in Greek; Fig. 2.2-43). Most often affects the extremities and trunk. Patients experience a worsening of symptoms in dry, cold weather.

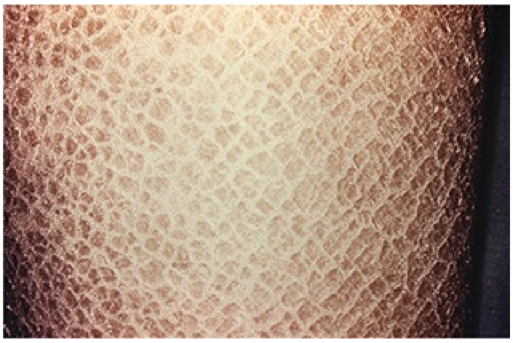


FIGURE 2.2-43. **Ichthyosis vulgaris.** (Reproduced with permission from Dr. Richard S. Hibbets, Centers for Disease Control and Prevention, Atlanta, GA.)

- Inherited mutation in filaggrin gene; worse in homozygous individuals. Filaggrin plays a role in maintaining hydration of the skin with an epidermal skin barrier.
- Diagnosis is clinical.
- Treat with emollients and moisturizers.

AGE-RELATED SKIN CHANGES

The elastic fibers in perivascular connective tissue deteriorate with age, causing wrinkles. The dermis and epidermis also thin, causing increased fragility of the skin. Chronically photoaged skin will develop solar elastosis (thickened yellow skin with deep wrinkles).

Botulinum toxin A may be used for cosmetic purposes to reduce development of wrinkles (paralysis of facial musculature). Senile purpura (ecchymoses in older adult patients in areas exposed to repetitive trauma such as extensor surfaces) is a benign finding and does not warrant further workup.

SUN PROTECTION

UV radiation from the sun causes hyperpigmentation and destruction of dermal structural proteins, such as collagen and elastin. Sun avoidance is the best way to prevent sun-associated skin damage. Sunblock with a sun protection factor (SPF) of at least 30 applied 30 minutes prior to exposure provides a protective film that prevents sunburn. SPF of greater than 50 has diminishing returns on effective sun protection. Reapplication of sunblock should occur every 2 hours, especially after swimming or sweating.

SUNBURN

Self-limiting, inflammatory skin condition occurring in response to prolonged exposure to UV radiation. Vasodilation of dermal blood vessels causes an erythematous appearance to the skin and occasionally blistering lesions. Patients with severe sunburn may exhibit symptoms of heat exhaustion such as fever, headache, and vomiting. Mild sunburn may be treated with cool, moist compresses and emollients with aloe vera for topical relief and NSAIDs for pain relief. Consider hospitalization, IV fluids, and wound care for severe cases.

medpox.com

NEOPLASMS OF THE SKIN

SEBORRHEIC KERATOSIS

A very common skin tumor in people older than 50 years of age. Unknown etiology. Though lesions may appear similar to melanoma, they have no malignant potential.

History/PE

- Present as exophytic, waxy, brown papules and velvety or greasy plaques with superficial keratin cysts (Fig. 2.2-44). Lesions may appear in great numbers and have a "stuck on" appearance.

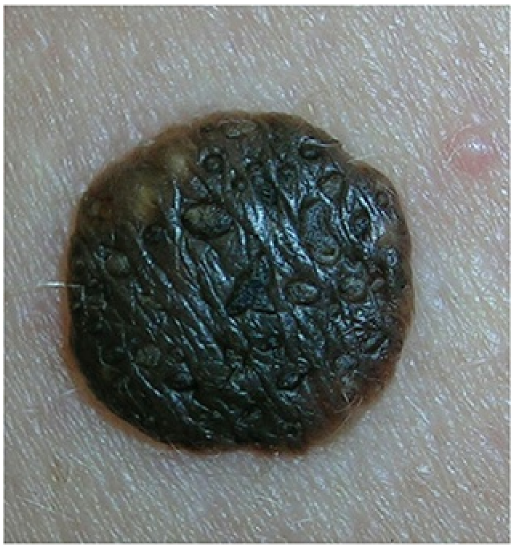


FIGURE 2.2-44. **Seborrheic keratosis.** Waxy brown papule with a “stuck on” appearance. (Reproduced with permission from Dr. Richard Usatine.)

- Lesions can become irritated either spontaneously or by external friction trauma.

Diagnosis

Clinical diagnosis. Malignancy can be ruled out with biopsy.

KEY FACT

Leser-Trelat sign is the sudden appearance of multiple seborrheic keratoses in a “Christmas tree” pattern on the back (Fig. 2.2-45). It is associated with internal malignancy, most commonly gastric adenocarcinoma.

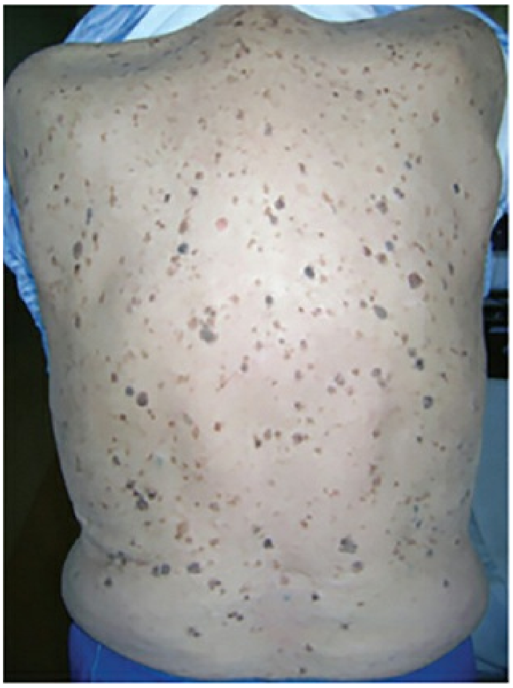


FIGURE 2.2-45. **Leser-Trelat sign.** (Image modified with permission from Ponti G, Luppi G, Losi L, Giannetti A, Seidenari S. Leser-Trélat syndrome in patients affected by six multiple metachronous primitive cancers. *J Hematol Oncol.* 2010;3:2. doi:10.1186/1756-8722-3-2.)

Treatment

Cryotherapy, shave excision, or curettage.

ACTINIC KERATOSIS

Flat areas of erythema and scale caused by sun exposure in fair-skinned individuals. These lesions have a 5% to 10% chance of developing into squamous cell carcinoma (SCC). Lesions must be treated before progression to malignancy.

- ***Hx/PE:*** Lesions appear on sun-exposed areas (face, arms) and primarily affect older patients, who often have multiple such lesions. They are erythematous with a sandpaper-like texture that can become thick and crusted (Fig. 2.2-46).

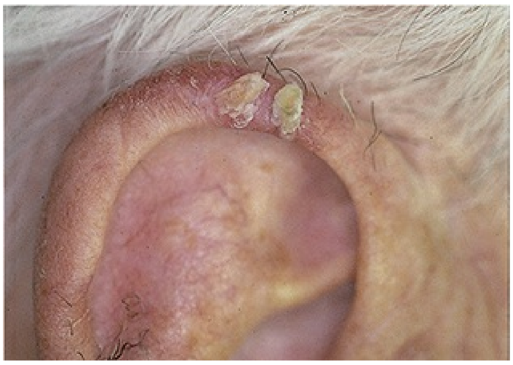


FIGURE 2.2-46. **Actinic keratosis.** The discrete patch above has an erythematous base and a rough white scale. (Reproduced with permission from Hurwitz RM. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation.* 2nd ed. Stamford, CT: Appleton & Lange; 1998.)

- ***Dx:*** Clinical. Biopsy may be indicated to differentiate from SCC.
- ***Tx:*** Cryosurgery, topical 5-FU, or topical imiquimod can be used to destroy the lesion. Patients should be advised to use sun protection.

CUTANEOUS SQUAMOUS CELL CARCINOMA

The second most common skin cancer, with locally destructive effects as well as the potential for metastasis and death. Sun exposure is the most common causative factor, but exposure to chemical carcinogens, prior radiation therapy, chronic inflammation and chronic wounds (eg, burns or draining infectious sinuses in osteomyelitis), and chronic immunosuppression (eg, transplant recipients) also predispose patients to developing SCC. Keratoacanthomas are a low-grade type of SCC.

History/PE

- SCCs have many forms, and a single patient will often have multiple variants.
- Most SCCs occur in older adults with sun-damaged skin arising from actinic keratoses and presenting as an erythematous, ulcerated papule or nodule (Fig. 2.2-47).

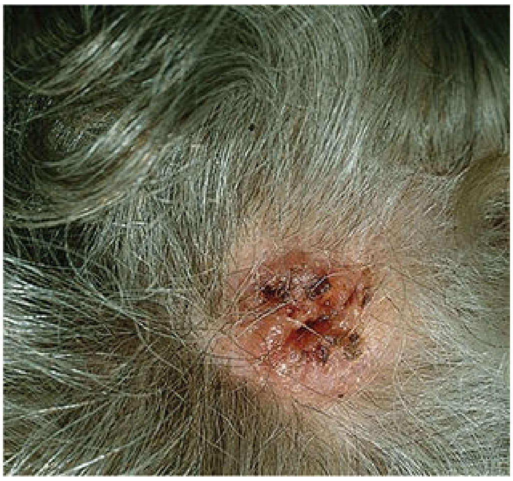


FIGURE 2.2-47. **Squamous cell carcinoma.** Note the crusting and ulceration of this erythematous plaque. Most lesions are exophytic nodules with erosion or ulceration. (Reproduced with permission from Hurwitz RM. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation.* 2nd ed. Stamford, CT: Appleton & Lange; 1998.)

- Neurologic signs/symptoms may be due to perineural invasion.
- Marjolin ulcer is a type of rare SCC that arises in sites of scars, burns, or ulcers. Marjolin ulcers typically take 5 to 10 years to develop after the initial wound.
- Arsenic exposure is a rare cause of multiple SCCs in a palmoplantar distribution.
- SCC in situ is called Bowen disease and presents as a well-defined, erythematous, scaly plaque. When found on the penis, it is called erythroplasia of Queyrat and presents as red, velvetlike plaques.
- SCCs from actinic keratoses rarely metastasize, but those that arise on the lips and ulcers are more likely to do so. SCC occurs on the lower lip more commonly than basal cell carcinoma (BCC).

Diagnosis

Characteristic exam findings and history are sufficient. Confirm with shave biopsy, which may show keratin pearls and full-thickness atypical keratinocytes with invasion into the dermis.

Treatment

Surgical excision or Mohs surgery (very thin slices are excised and examined with a microscope via frozen section, ideally used for cosmetically sensitive areas such as face and distal extremities). Lesions with high metastatic potential may need radiation or chemotherapy.

BASAL CELL CARCINOMA

The most common malignant skin cancer, BCC is slow growing and locally destructive but has virtually no metastatic potential. Cumulative sun exposure is the main risk factor. Most lesions appear on the face in fair-skinned individuals. Multiple BCCs appearing early in life and on non–sun-exposed areas are suggestive of inherited basal cell nevus syndrome (Gorlin syndrome).

History/PE

Nodular subtype (Fig. 2.2-48) makes up 80% of BCC. Other types include superficial and sclerosing. Pearly-white, translucent, dome-shaped nodule or papule that may ulcerate, bleed, or crust in the center with overlying telangiectasias.

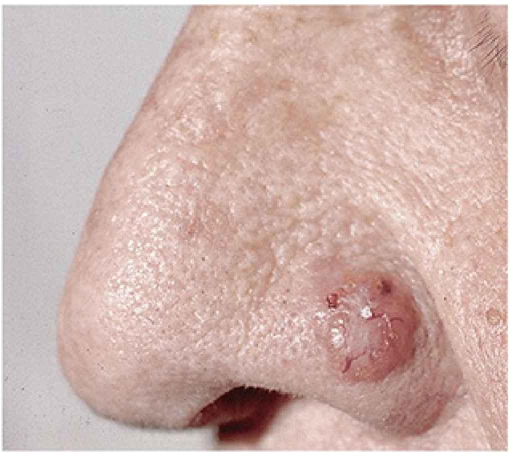


FIGURE 2.2-48. **Nodular basal cell carcinoma.** A smooth, pearly nodule with telangiectasias. (Reproduced with permission from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology.* 5th ed. New York, NY: McGraw-Hill; 2005.)

Diagnosis

Confirm with shave biopsy, which will show nests of basophilic cells invading into the dermis.

Treatment

Excision via curettage, cautery, cryotherapy, and superficial radiation. Mohs surgery can be used for cosmetically sensitive areas.

MNEMONIC

The ABCDEs of melanoma—

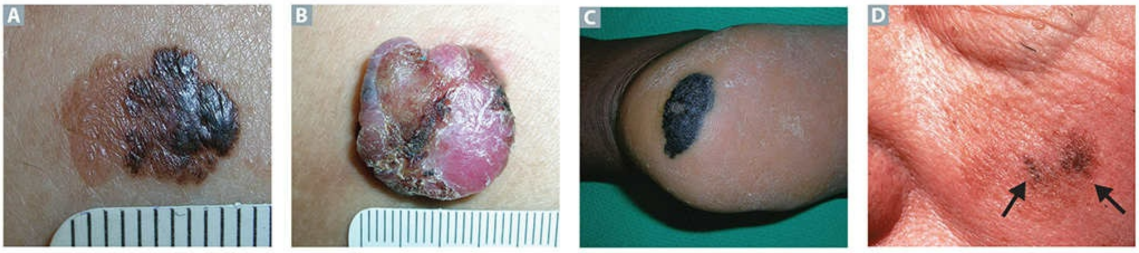
Asymmetric
Irregular **B**order
Variations in **C**olor
Diameter >6 mm
Evolution: changing or new lesions

MELANOMA

The most common life-threatening dermatologic disease. Risk factors include fair skin and a tendency to burn; intense bursts of sun exposure (especially in childhood and with intermittent exposure); and the presence of large congenital melanocytic nevi, an ↑ number of nevi, or dysplastic nevi. Immunosuppression also ↑ risk. Some patients inherit a predisposition to melanoma with the familial atypical mole and melanoma (FAM-M) syndrome. There are several subtypes (Table 2.2-5).

TABLE 2.2-5. **Types of Melanoma**

TYPE	PRESENTATION
Superficial spreading	60% of all melanomas; incidence increases with age, but is also seen in young adults Often presents on the trunk in men and on the legs in women A prolonged horizontal growth phase (see Image A) allows for early diagnosis when it is still confined to the epidermis
Nodular	Lesions have a rapid vertical growth phase and appear as a fast-growing reddish-brown nodule with ulceration (see Image B)
Acral lentiginous	Begins on the palms, soles (see Image C), and nailbed as a slowly spreading, pigmented patch Most commonly seen in Asian and Black populations
Lentigo maligna	Arises in a solar lentigo Usually found on sun-damaged skin of the face (see Image D)
Amelanotic	Presents as a lesion without clinical pigmentation Difficult to identify; this variant of melanoma can be further classified into any of the above types



Images reproduced with permission from Dr. Richard Usatine.

History/PE

- Malignant melanomas begin in the epidermal basal layer, where melanocytes are found.
- Malignant melanomas may metastasize anywhere in the body (eg, lung, liver, brain, fat). Three to five percent of patients with metastatic melanoma have no known primary lesion.

Q

A 72-year-old man presents to an internist after moving to Florida. The internist notes a chronic wound on the patient’s right lower leg in the area of a previous flame burn. The patient states that the wound has been present for 5 years and has not healed despite receiving dressings and topical treatment. What is the next best step?

Diagnosis

- Early recognition and treatment are essential. Screening exams using the ABCDE criteria and dermoscopy may detect melanoma early when it is curable (see Table 2.2-5). An excisional biopsy should be performed on any suspicious lesion. Malignancy is determined histologically.
- A biopsy should be performed on a mole that is substantially different from nearby moles to assess for melanoma. This is the “ugly duckling sign” and has greater than 90% sensitivity for melanoma.
- Malignant melanomas are staged by Breslow thickness (depth of invasion in millimeters) and by tumor-node-metastasis (TNM) staging. Ulceration is a poor prognostic sign.

Treatment

- Lesions confined to the skin are treated by excision with margins. Sentinel lymph node biopsy is useful for staging but does not ↑ survival. Chemotherapy, biologic therapy, and radiation therapy may be used for recurrent or metastatic melanoma.

- Patients with early melanoma are at low risk for recurrence but are at high risk for the development of subsequent melanomas. More advanced melanomas may recur or metastasize at a higher rate. Patient surveillance is thus essential.

A

The next best step would be to perform a biopsy to rule out SCC.

KAPOSI SARCOMA

A vascular proliferative disease that has been attributed to HHV-8, also called Kaposi sarcoma–associated herpesvirus (KSHV).

History/PE

- Presents with multiple red to violaceous macules, papules, or nodules that can progress to plaques on the lower limbs, back, face, mouth, and genitalia (Fig. 2.2-49).

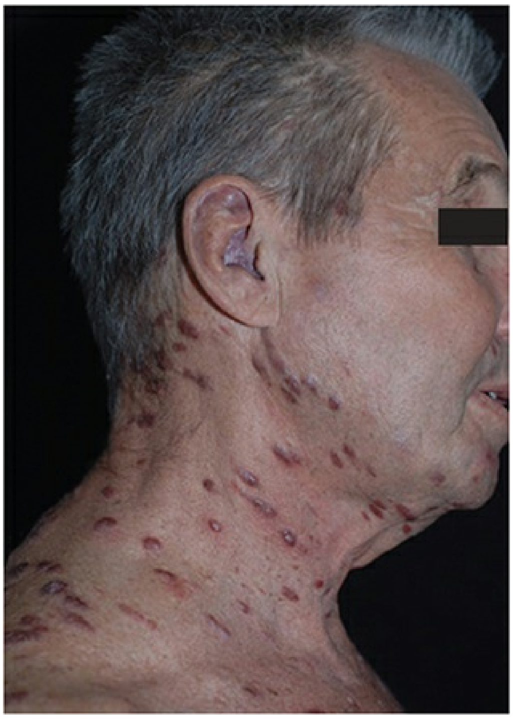


FIGURE 2.2-49. Kaposi sarcoma. Note the multiple violaceous papules on the neck, back, and face. (Reproduced with permission from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*. 5th ed. New York, NY: McGraw-Hill; 2005.)

- Plaques can also be found in the GI tract and lung.
- HIV-associated (epidemic) Kaposi sarcoma is an aggressive form of the disease, and although less common since the advent of highly active antiretroviral therapy (HAART), it remains the most common HIV-associated malignancy.

Diagnosis

Diagnosed by history, clinical impression, and histology.

Treatment

Start HAART therapy if patient is HIV⊕. Small local lesions can be treated with radiation or cryotherapy. Widespread or internal disease is treated with systemic chemotherapy (doxorubicin, paclitaxel, or interferon-α [IFN-α]).

KEY FACT

Bacillary angiomatosis, caused by ***Bartonella henselae*** and ***Bartonella quintana,*** can mimic Kaposi sarcoma and should be excluded in suspected Kaposi sarcoma patients; erythromycin is the treatment of choice.

MYCOSIS FUNGOIDES (CUTANEOUS T-CELL LYMPHOMA)

Not a fungus but a slow, progressive neoplastic proliferation of epidermotropic T cells. The disease is chronic and more common in men.

History/PE

- Early lesions are nonspecific, psoriatic-appearing plaques or patches that are often pruritic with a predilection for the trunk and buttocks. Later lesions are characterized by skin tumors with palpable lymph nodes (Fig. 2.2-50).

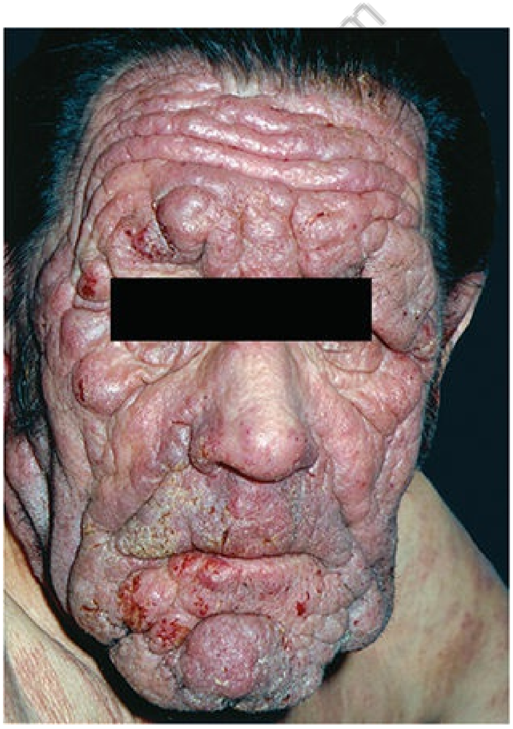


FIGURE 2.2-50. **Mycosis fungoides.** Massive nodular infiltration of the face leads to a leonine facies. (Reproduced with permission from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine*. 7th ed. New York, NY: McGraw-Hill; 2008.)

- Patients may have dermatopathic lymphadenopathy without tumor involvement of the node. However, the internal organs can be involved, including the lymph nodes, liver, and spleen.
- Sézary syndrome is the leukemic phase of cutaneous T-cell lymphoma, characterized by circulating Sézary cells in the peripheral blood, erythroderma, and lymphadenopathy.

Diagnosis

- Diagnosed by clinical features and histology, with immunophenotypic characterization showing clonal T cells and electron microscopy showing the typical Sézary or Lutzner cells (cerebriform lymphocytes).
- Early lesions are clinically indistinguishable from dermatitis, so histologic diagnosis is indicated for any dermatitis that is chronic and resistant to treatment.

Treatment

Phototherapy and skin-directed topical treatments are the mainstay of treatment for many patients. Early localized disease is amenable to total skin electron beam irradiation. For more extensive or advanced disease, radiation therapy is an effective option. Treatment modalities, including steroids, chemotherapy, retinoids, monoclonal antibodies, and IFN-α, are often combined.

CHERRY ANGIOMAS (HEMANGIOMAS)

Small, vascular, red papules that can appear anywhere on the body (Fig. 2.2-51). It is the most common benign vascular tumor, and it often appears with age. No treatment is necessary, but it can be excised for cosmetic reasons.

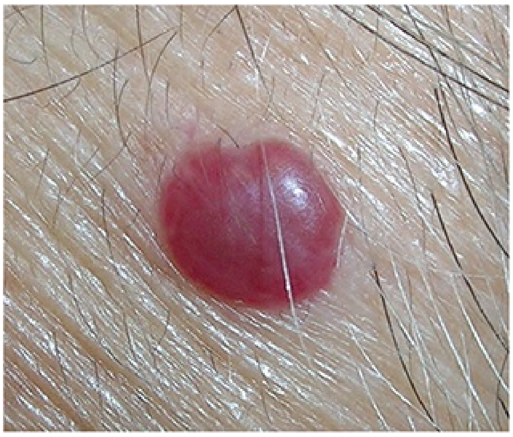


FIGURE 2.2-51. Cherry hemangioma. (Reproduced with permission from Dr. Richard Usatine.)

INFANTILE HEMANGIOMAS

Similar to cherry angiomas, infantile hemangiomas (also called strawberry hemangiomas) are seen in infants during the first few weeks of life. They are also benign and usually regress spontaneously after an initially rapid growth phase. Involution typically begins at 9 months to 1 year of age. Persistent lesions may be treated with topical or oral β-blockers.

PYOGENIC GRANULOMA

Lobulated capillary hemangioma that typically occurs on the fingers, trunk and oral mucosa in young adults (Fig. 2.2-52). Ulcerates and bleeds profusely. Associated with trauma and pregnancy likely due to increased vascular endothelial growth factor (VEGF) in pregnancy. Treated via surgical excision, laser therapy, or topical silver nitrate. Lesions that occur during pregnancy may regress spontaneously postpartum.

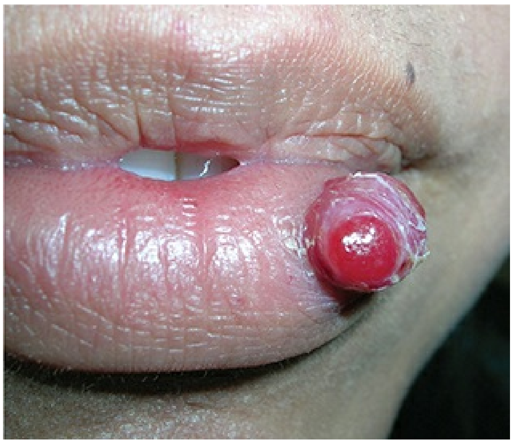


FIGURE 2.2-52. **Pyogenic granuloma.** (Modified with permission from Dr. Richard Ustaine.)

NECROBIOSIS LIPOIDICA

Red-brown to yellow annular plaques found on the lower extremities of patients with DM (Fig. 2.2-53). More common in women and classically found on pretibial skin. Presents as multifocal lesions with dilated blood vessels and central epidermal atrophy that may ulcerate. Lesions may precede the onset of diabetes; consequently, patients should be screened for DM.

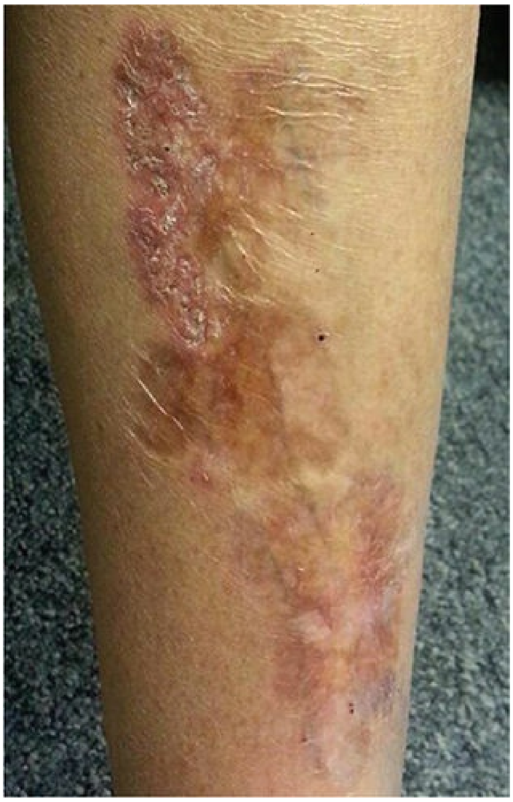


FIGURE 2.2-53. **Necrobiosis lipoidica.** (Reproduced with permission from Pathak R, Karmacharya P, Aryal MR, Smith-Coleman KE. Necrobiosis lipoidica. *J Community Hosp Intern Med Perspect.* 2013;3-4. doi:10.3402/jchimp.v3i3-4.22627.)

HIGH-YIELD FACTS IN

ENDOCRINOLOGY

Disorders of Glucose Metabolism
  METABOLIC SYNDROME
  DIABETES MELLITUS
  DIABETIC KETOACIDOSIS AND HYPERGLYCEMIC HYPEROSMOLAR SYNDROME
  HYPOGLYCEMIA

Thyroid Disorders
  THYROID PHYSIOLOGY
  HYPERTHYROIDISM AND THYROTOXICOSIS
  HYPOTHYROIDISM
  THYROIDITIS
  THYROID NEOPLASMS

Bone and Mineral Disorders
  OSTEOPOROSIS
  PAGET DISEASE OF BONE
  HYPERPARATHYROIDISM

Pituitary and Hypothalamic Disorders
  DEFICIENCY OF PITUITARY HORMONES
  DIABETES INSIPIDUS
  EXCESS OF PITUITARY HORMONES
  HYPERPROLACTINEMIA
  SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

Adrenal Gland Disorders
  ADRENAL INSUFFICIENCY
  PHEOCHROMOCYTOMA
  CUSHING SYNDROME
  HYPERALDOSTERONISM
  CONGENITAL ADRENAL HYPERPLASIA

Multiple Endocrine Neoplasias

DISORDERS OF GLUCOSE METABOLISM

METABOLIC SYNDROME

Metabolic syndrome refers to a constellation of findings suggestive of insulin resistance that frequently develop in the setting of obesity. The often-associated hyperinsulinemia, hyperglycemia, and release of adipokines are thought to increase risk for development of atherosclerotic cardiovascular disease and type 2 diabetes mellitus (DM).

MNEMONIC

WEIGHHT

Waist **E**xpanded, **I**mpaired **G**lucose, **H**ypertension, **H**DL ↓, **T**riglycerides ↑

History/PE

Abdominal obesity (even in the setting of overall normal weight), acanthosis nigricans, and elevated blood pressure.

Diagnosis

At least three of the following five criteria must be met:

- Abdominal obesity
- Elevated fasting glucose
- Hypertension
- Low HDL cholesterol
- Hypertriglyceridemia

Treatment

- Best initial treatment is lifestyle modification.
- Mitigation of cardiovascular risk can occur with aggressive cholesterol management and blood pressure (BP) control, as well as initiation of metformin for prevention of diabetes in those with impaired fasting glucose.

DIABETES MELLITUS

DM refers to abnormal carbohydrate metabolism that leads to hyperglycemia through several mechanisms, including impairment of insulin secretion and resistance of peripheral tissues to the action of insulin.

History/PE

The presentation of diabetes is variable (often asymptomatic), and it depends on the specific etiology. Generally:

- Type 1 DM classically presents in children and young adults with symptoms of hyperglycemia (polyuria, polydipsia), polyphagia, unexplained weight loss, or ketoacidosis.
- Type 2 DM classically presents in older adults with obesity and other components of metabolic syndrome, but it is increasingly diagnosed in children. Other risk factors include ⊕ family history, sedentary lifestyle, increasing age, and ethnicity (Asian, Hispanic, and African descent in the United States). Although it may present with symptoms of hyperglycemia—in the same manner as type 1 DM—it tends to be more insidious, and patients frequently exhibit complications of long-term diabetes (see Table 2.3-1) at time of diagnosis.

TABLE 2.3-1. **Chronic Complications of Diabetes Mellitus**

COMPLICATION	DESCRIPTION, MANAGEMENT, AND PREVENTIVE CARE
Retinopathy (non-proliferative, proliferative)	Classically appears when diabetes has been present for at least 3–5 years (see Fig. 2.3-1). Preventive measures include control of hyperglycemia and hypertension and annual eye exams. Treatment modalities include anti–vascular endothelial growth factor (VEGF) agents and laser photocoagulation therapy.
Diabetic nephropathy	Characterized by glomerular hyperfiltration followed by microalbuminuria, macroproteinuria, and progression to chronic kidney disease (CKD). Prevalence is estimated to be 20%–40% in those with DM. Preventive measures include glycemic control, tight BP control (angiotensin-converting enzyme inhibitors [ACEIs] and angiotensin receptor blockers [ARBs] in the setting of proteinuria). Kimmelstiel-Wilson nodules are classically seen on kidney biopsy.
Neuropathy	Prevalence of diabetic neuropathy increases with longer duration/worsening severity of hyperglycemia. Can affect both small nerve fibers (pain, temperature) and large fibers (vibration, proprioception). Most commonly manifests as distal symmetric polyneuropathy ("stocking and glove" numbness, tingling, burning pain). Can also present as autonomic neuropathy (postural hypotension, gastroparesis, diarrhea, neurogenic bladder, erectile dysfunction). Cranial mononeuropathies can also occur—cranial nerve (CN) III involvement is more common (ptosis, diplopia, preserved pupil response). Emphasize preventive foot care. Monofilament testing predicts ulcer risk. Neuropathic pain can be managed with tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), or gabapentinoids. Gastroparesis with delayed gastric emptying can be managed with metoclopramide or erythromycin.
Macrovascular complications	Cardiovascular, cerebrovascular, and peripheral vascular disease. Cardiovascular disease is the most common cause of death in diabetic patients. See Table 2.3-2 for risk modification recommendations.
Hypoglycemia unawareness	Inadequate autonomic response to hypoglycemia caused by insufficient release of stress hormones. It tends to develop in people who have frequent episodes of hypoglycemia, and it can lead to failure to recognize life-threatening hypoglycemia.

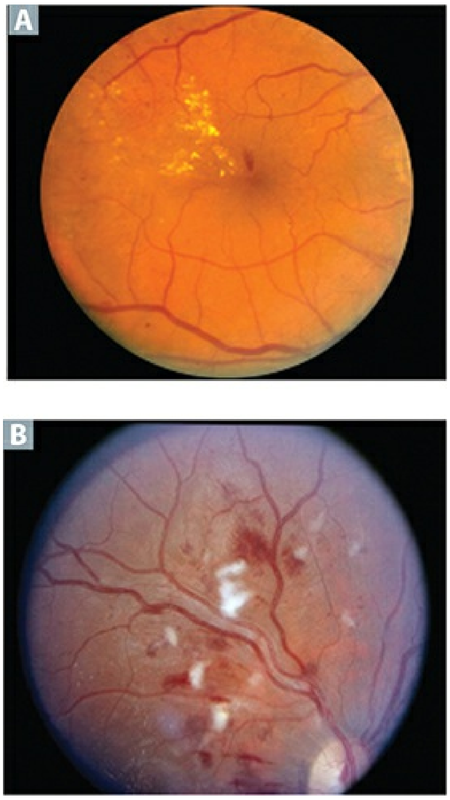


FIGURE 2.3-1. **Diabetic retinopathy. (A)** Nonproliferative retinopathy presents with exudates, dot-blot hemorrhages, and microaneurysms. **(B)** Proliferative retinopathy presents with macular edema, vitreous traction, and neovascularization of the retinal vasculature. (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

Microalbuminuria cannot be detected on routine urinalysis (UA) protein dipstick. Instead, do a spot urine albumin to creatinine ratio (microalbuminuria = 30 to 300 mg/g).

Diagnosis

Diagnosis requires:

- A random plasma glucose level ≥200 mg/dL plus symptoms of hyperglycemia

OR two abnormal results with any of the following tests:

- A fasting (>8-hour) plasma glucose level ≥126 mg/dL
- A 2-hour postprandial glucose level ≥200 mg/dL following an oral glucose tolerance test (OGTT)
- Hemoglobin A1c (HbA1c) >6.5%

Consider screening for type 2 DM in:

- Overweight adults with at least one risk factor for DM (hypertension, cardiovascular disease [CVD], sedentary lifestyle, dyslipidemia, polycystic ovary syndrome [PCOS], first-degree relative with DM).
- Patients planning pregnancy.
- Patients on medications that increase risk for DM (chronic steroids, HIV medications, antipsychotics).
- In all people aged 45 years or older, check HbA1c—if <5.7, recheck every 3 years (unless other risk factors develop). If between 5.7 and 6.4, recheck yearly.

Patients not meeting criteria for DM but with impaired fasting glucose (>100 but <126 mg/dL) or impaired glucose tolerance on OGTT should also be rechecked yearly.

Classification

Type I DM is due to destruction of beta cells of the pancreas, which normally produce insulin. This can be secondary to:

- Autoimmune disease—characterized by the presence of autoantibodies (anti–glutamic acid decarboxylase [GAD], anti-islet cell, anti-zinc transporter, anti-insulin antibodies). Associated with human leukocyte antigen (HLA)-DR3 and HLA-DR4.
- Acquired disease—after pancreatitis, pancreatectomy, cystic fibrosis, or malignancy.
- Idiopathic disease—in the absence of antibodies or recognized destructive disease.

Type II DM is due to relative insulin deficiency in the setting of peripheral insulin resistance, leading to hyperglycemia. More than 90% of DM cases are classified as type 2. Antibodies associated with type 1 DM will be negative.

Other less common etiologies of DM include several genetic defects that affect beta-cell function. For example, several autosomal monogenetic defects have been identified as causes of maturity-onset diabetes of the young (MODY), which typically presents in young people with a family history of atypical diabetes.

Management

- Patient education and lifestyle modification are mainstays of management (see Table 2.3-2).

TABLE 2.3-2. **Diabetes Mellitus General Health Maintenance**

LIFESTYLE MODIFICATIONS	RECOMMENDATION
Diet	Personalized diet to encourage weight loss; avoid saturated fats and added sugars.
Exercise	Moderate-intensity exercise for 30–60 minutes 5 days per week.
Cardiovascular risk modification	The presence of diabetes is equivalent to the highest risk for cardiovascular disease regardless of all other risk factors. All diabetic patients 40–75 years of age should be placed on a statin regardless of lipid levels. Use the AHA risk calculator to determine whether moderate or high-intensity statin is recommended.[a]
Blood pressure (BP) management	Strict BP control to <130/80 mm Hg; ACEIs/ARBs are first-line agents when proteinuria is present.
Screening exams	Annual physical exam to screen for cardiovascular disease (BP and lipid monitoring), nephropathy (test for microalbuminuria), retinopathy (dilated-eye exams), and neuropathy (foot care evaluations).
Immunizations	In addition to routinely recommended immunizations based on age, all patients with diabetes >19 years of age should receive the pneumonia vaccine.

- Type 1 DM requires administration of insulin (see Fig. 2.3-2) to maintain blood glucose in the normal range (80–130 mg/dL preprandial levels, <180 mg/dL postprandial levels).

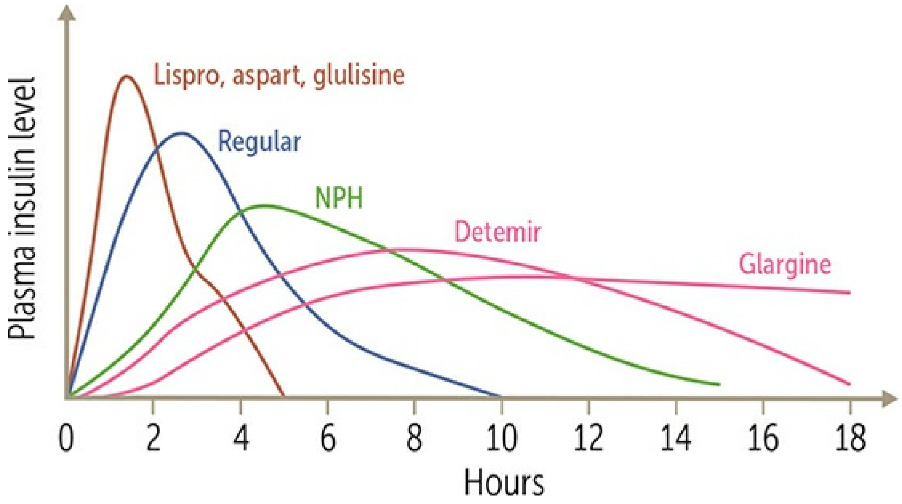
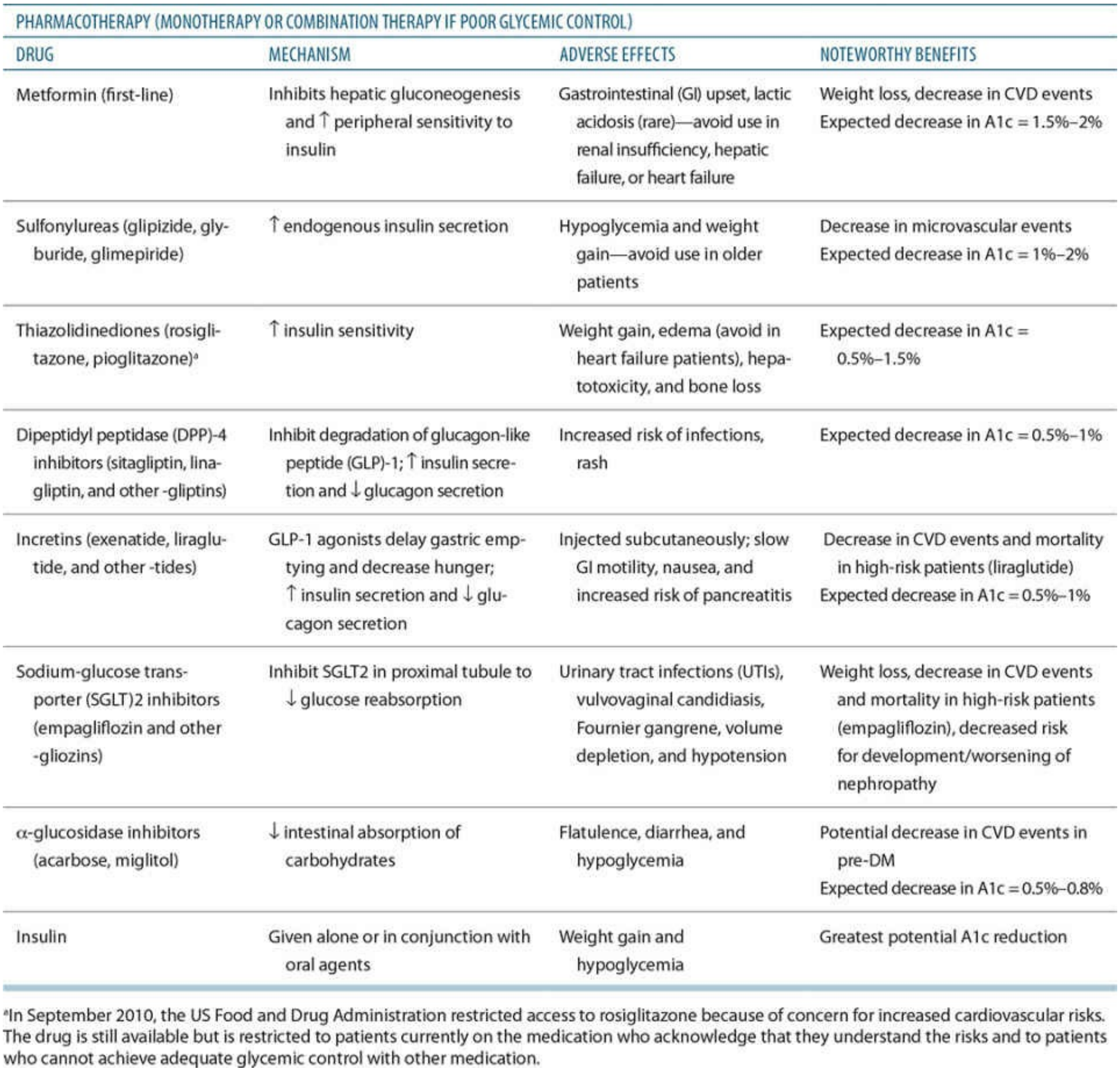


FIGURE 2.3-2. **Pharmacokinetics of insulin preparations.** Short acting (aspart, lispro, glulisine): onset in 5–20 minutes, peak in 0.5–3 hours, duration 3–8 hours. Regular: onset in 30 minutes, peak in 2–4 hours, duration 5–8 hours. Neutral Protamine Hagedorn (NPH) insulin: onset in 2–4 hours, peak in 6–10 hours, duration 18–28 hours. Long acting (detemir,

glargine): onset in 2 hours, peak none, duration 20–24 hours. (Reproduced with permission from USMLE-Rx.com.)

- Consider insulin infusion pump for patients with type 1 DM who are having difficulty with intermittent dosing.
- Type 2 DM can be managed with nonpharmacologic interventions initially. In the event of failure of lifestyle interventions, a number of medication classes can be considered (see Table 2.3-3).

TABLE 2.3-3. **Treatment of Type 2 Diabetes Mellitus**



PHARMACOTHERAPY (MONOTHERAPY OR COMBINATION THERAPY IF POOR GLYCEMIC CONTROL)			
DRUG	MECHANISM	ADVERSE EFFECTS	NOTEWORTHY BENEFITS
Metformin (first-line)	Inhibits hepatic gluconeogenesis and ↑ peripheral sensitivity to insulin	Gastrointestinal (GI) upset, lactic acidosis (rare)—avoid use in renal insufficiency, hepatic failure, or heart failure	Weight loss, decrease in CVD events Expected decrease in A1c = 1.5%–2%
Sulfonylureas (glipizide, glyburide, glimepiride)	↑ endogenous insulin secretion	Hypoglycemia and weight gain—avoid use in older patients	Decrease in microvascular events Expected decrease in A1c = 1%–2%
Thiazolidinediones (rosiglitazone, pioglitazone)[a]	↑ insulin sensitivity	Weight gain, edema (avoid in heart failure patients), hepatotoxicity, and bone loss	Expected decrease in A1c = 0.5%–1.5%
Dipeptidyl peptidase (DPP)-4 inhibitors (sitagliptin, linagliptin, and other -gliptins)	Inhibit degradation of glucagon-like peptide (GLP)-1; ↑ insulin secretion and ↓ glucagon secretion	Increased risk of infections, rash	Expected decrease in A1c = 0.5%–1%
Incretins (exenatide, liraglutide, and other -tides)	GLP-1 agonists delay gastric emptying and decrease hunger; ↑ insulin secretion and ↓ glucagon secretion	Injected subcutaneously; slow GI motility, nausea, and increased risk of pancreatitis	Decrease in CVD events and mortality in high-risk patients (liraglutide) Expected decrease in A1c = 0.5%–1%
Sodium-glucose transporter (SGLT)2 inhibitors (empagliflozin and other -gliozins)	Inhibit SGLT2 in proximal tubule to ↓ glucose reabsorption	Urinary tract infections (UTIs), vulvovaginal candidiasis, Fournier gangrene, volume depletion, and hypotension	Weight loss, decrease in CVD events and mortality in high-risk patients (empagliflozin), decreased risk for development/worsening of nephropathy
α-glucosidase inhibitors (acarbose, miglitol)	↓ intestinal absorption of carbohydrates	Flatulence, diarrhea, and hypoglycemia	Potential decrease in CVD events in pre-DM Expected decrease in A1c = 0.5%–0.8%
Insulin	Given alone or in conjunction with oral agents	Weight gain and hypoglycemia	Greatest potential A1c reduction

[a] In September 2010, the US Food and Drug Administration restricted access to rosiglitazone because of concern for increased cardiovascular risks. The drug is still available but is restricted to patients currently on the medication who acknowledge that they understand the risks and to patients who cannot achieve adequate glycemic control with other medication.

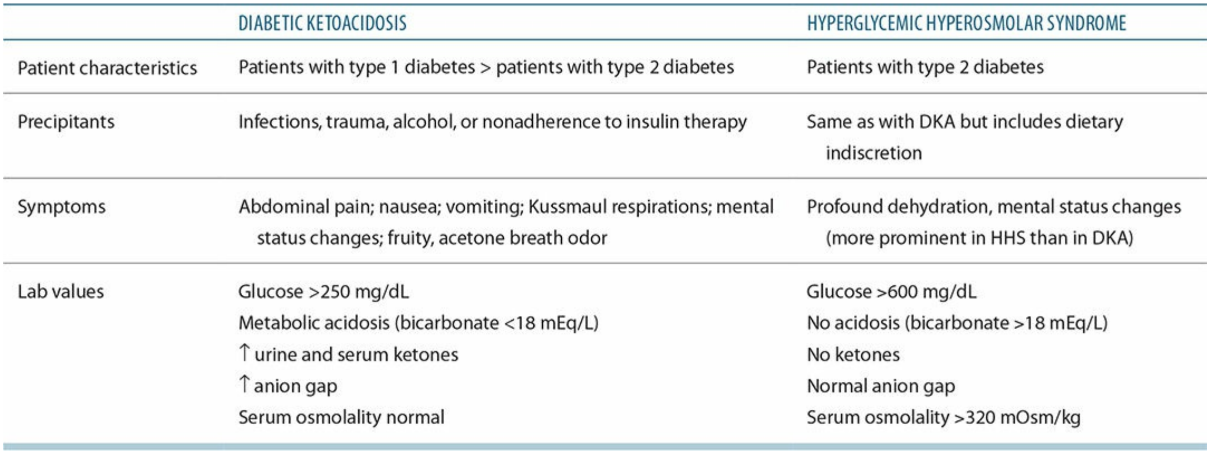
- All patients on insulin should participate in self-monitoring of blood glucose to detect hyperglycemia or hypoglycemia that can be corrected with dose modifications.
- Patients with DM should be encouraged to undergo routine HbA1c testing every 3 months.
- Goal HbA1c <7% (<7.5% in children). Higher blood glucose and HbA1c levels can be tolerated, particularly in the older adult population and in those with multiple medical problems, considering the ↑ risk for hypoglycemia. Tight glucose control decreases the risk for microvascular complications (nephropathy, retinopathy), but the effects on macrovascular complications (stroke, myocardial infarction) and all-cause mortality are

unknown.

DIABETIC KETOACIDOSIS AND HYPERGLYCEMIC HYPEROSMOLAR SYNDROME

These are two acute, life-threatening complications of diabetes that are characterized by hyperglycemia with fluid and electrolyte disturbances. Table 2.3-4 outlines the individual characteristics of each.

TABLE 2.3-4. Acute Complications of Diabetes Mellitus: Diabetic Ketoacidosis vs Hyperglycemic Hyperosmolar Syndrome



	DIABETIC KETOACIDOSIS	HYPERGLYCEMIC HYPEROSMOLAR SYNDROME
Patient characteristics	Patients with type 1 diabetes > patients with type 2 diabetes	Patients with type 2 diabetes
Precipitants	Infections, trauma, alcohol, or nonadherence to insulin therapy	Same as with DKA but includes dietary indiscretion
Symptoms	Abdominal pain; nausea; vomiting; Kussmaul respirations; mental status changes; fruity, acetone breath odor	Profound dehydration, mental status changes (more prominent in HHS than in DKA)
Lab values	Glucose >250 mg/dL Metabolic acidosis (bicarbonate <18 mEq/L) ↑ urine and serum ketones ↑ anion gap Serum osmolality normal	Glucose >600 mg/dL No acidosis (bicarbonate >18 mEq/L) No ketones Normal anion gap Serum osmolality >320 mOsm/kg

- **Diabetic ketoacidosis (DKA)** is characterized by anion gap metabolic acidosis with elevated levels of ketoacids in serum and urine. Blood glucose level is usually between 250 and 500 mg/dL, but it can be higher.
- **Hyperglycemic hyperosmolar syndrome (HHS)** is characterized by extremely elevated blood glucose (frequently above 800–1000 mg/dL) and plasma hyperosmolality. Generally, there is no ketoacid accumulation and therefore no anion gap acidosis.

Management

Treatment of both entities is similar:

- Repletion of intravascular volume with infusion of normal saline. Patients with DKA/HHS are typically very dehydrated due to osmotic diuresis resulting from hyperglycemia.
- Frequent monitoring of serum electrolytes. Acidosis leads to extracellular shifting of potassium, which results in “normal” or “elevated” levels on initial labs despite an actual total body deficit. As insulin is infused (and as the acidosis is corrected), potassium shifts back into the intracellular space, leading to frank hypokalemia.
- Infusion of regular insulin intravenously if serum potassium is >3.3 mEq/L. Insulin should be infused until resolution of DKA/HHS (when anion gap closes and ketoacidosis is resolved in DKA, or until mental status improves to baseline in HHS). If potassium is <3.3mEq/L, insulin should be held and potassium infused until potassium is >3.3 mEq/L). If serum glucose reaches <200 mg/dL before resolution of acidosis (or <250 mg/dL in HHS), 5% dextrose can be administered intravenously to avoid stopping insulin infusion.

HYPOGLYCEMIA

Symptomatic hypoglycemia is very rare in people who are not on antihyperglycemic medications, even in the presence of a “low” blood sugar (<70 mg/dL). Further evaluation should only be carried out in patients who exhibit Whipple triad:

- Symptoms of hypoglycemia (tremor, anxiety, sweating, paresthesia, dizziness, weakness, confusion, loss of consciousness)
- A low plasma glucose concentration measured with a precise method while symptoms are present
- Relief of symptoms after blood glucose is raised

Causes of hypoglycemia include:

- Medications (accidental or purposeful antihyperglycemic medication overdose)
- Critical illness
- Cortisol insufficiency
- Insulinoma or non-insulinoma islet cell hypertrophy
- Recent history of gastric bypass (dumping syndrome)

Q

A 10-year-old boy presents to the emergency department (ED) with 2 weeks of polyuria and polydipsia and new-onset lethargy. Physical examination reveals signs of severe dehydration, and laboratory values reveal a blood glucose level of 500 mg/dL. After being diagnosed with DKA, the patient is started on insulin and non–dextrose-containing intravenous (IV) fluids. Glucose on recheck is 250 mg/dL with an anion gap of 19. What is the next best step in management?

Diagnosis

- Obtaining a detailed history is crucial. Careful questioning can ascertain timing of symptoms in relation to meals and medication administration. Patients with diabetes who are taking antihyperglycemics should have their medication regimen reviewed and medication doses reduced in cases of persistent hypoglycemia.
- If patients report symptoms after prolonged fasting, the physician may order an observed fast with periodic blood sugar assessment. Once symptoms arise, that is the time to obtain serum glucose, insulin, C-peptide, and antihyperglycemic drug screen.
- In patients who report symptoms shortly after meals, particularly in those with a history of gastric bypass, mixed-meal testing (consumption of a nonliquid meal with subsequent observation and monitoring of labs) can evaluate for dumping syndrome.
- If C-peptide levels are elevated, endogenous insulin is being produced. This is the case with insulin-secreting tumors or islet cell hypertrophy, insulin autoimmune hypoglycemia (in the presence of anti-insulin or anti-insulin receptor antibodies), or insulin secretagogue administration (⊕ drug screen).
- If C-peptide levels are low, there is exogenous insulin administration (possibly surreptitiously).

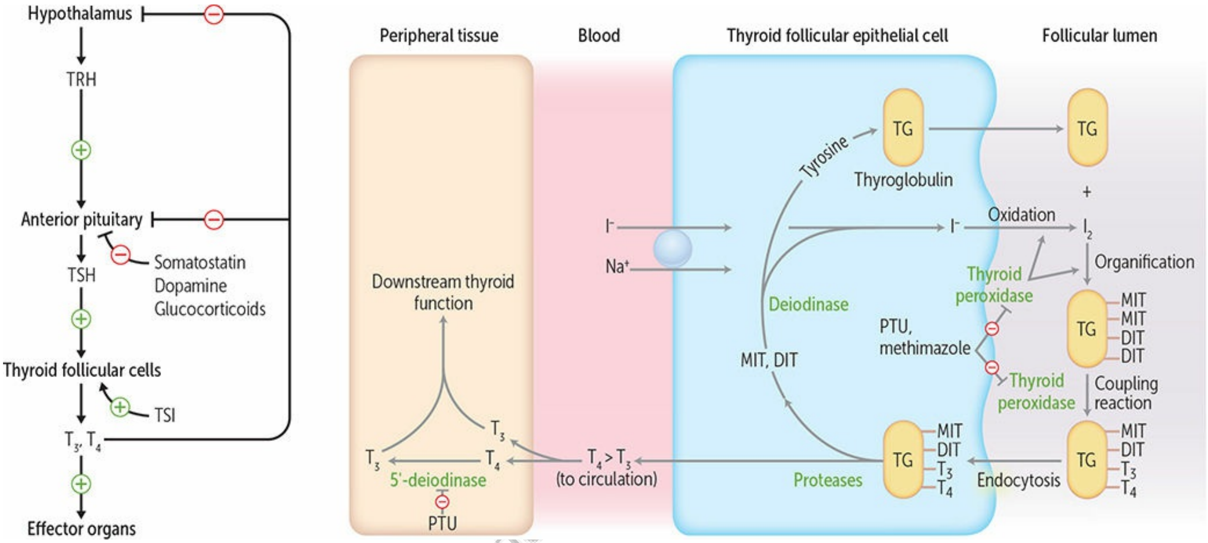
Management

After the cause of hypoglycemia is identified, management will be specific to the underlying etiology. Acute or profound hypoglycemia can be life-threatening, and it is most commonly seen in cases of overdosing of insulin or insulin secretagogues in people with diabetes. Rapid administration of oral or intravenous carbohydrates is the first step in management. In those with altered consciousness and no IV access, administer glucagon (intramuscular, intranasal, or subcutaneous formulations are available).

THYROID DISORDERS

THYROID PHYSIOLOGY

See Figure 2.3-3 for an overview of thyroid hormone synthesis and Figure 2.3-4 for a review of the hypothalamic-pituitary-thyroid axis.



Hypothalamus
TRH
Anterior pituitary
Somatostatin
Dopamine
Glucocorticoids
TSH
Thyroid follicular cells
TSI
T_3, T_4
Effector organs
Peripheral tissue
Blood
Thyroid follicular epithelial cell
Follicular lumen
Downstream thyroid function
T_3
T_3
T_4
5'-deiodinase
PTU
$T_4 > T_3$
(to circulation)
I^-
Na^+
Tyrosine
TG
Thyroglobulin
TG
I^-
Oxidation
+
I_2
Organification
Thyroid peroxidase
Deiodinase
PTU, methimazole
MIT, DIT
TG
MIT
MIT
DIT
DIT
Thyroid peroxidase
Coupling reaction
TG
MIT
DIT
T_3
T_4
Proteases
Endocytosis
TG
MIT
DIT
T_3
T_4

FIGURE 2.3-3. **Overview of thyroid synthesis and mechanism of antithyroid medications.** Iodide (I^-) is taken up from the bloodstream by follicular thyroid cells, transported to the colloid of the follicle, and oxidized to iodine (I). I combines with thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). Two DIT molecules combine to form T_4; MIT and DIT combine to form T_3. Iodinated thyroglobulin is transported back to the follicular cells and is cleaved in lysosomes; T_4 and T_3 are then released into the circulation. (Modified with permission from ScholarRx.com and USMLE-Rx.com.)

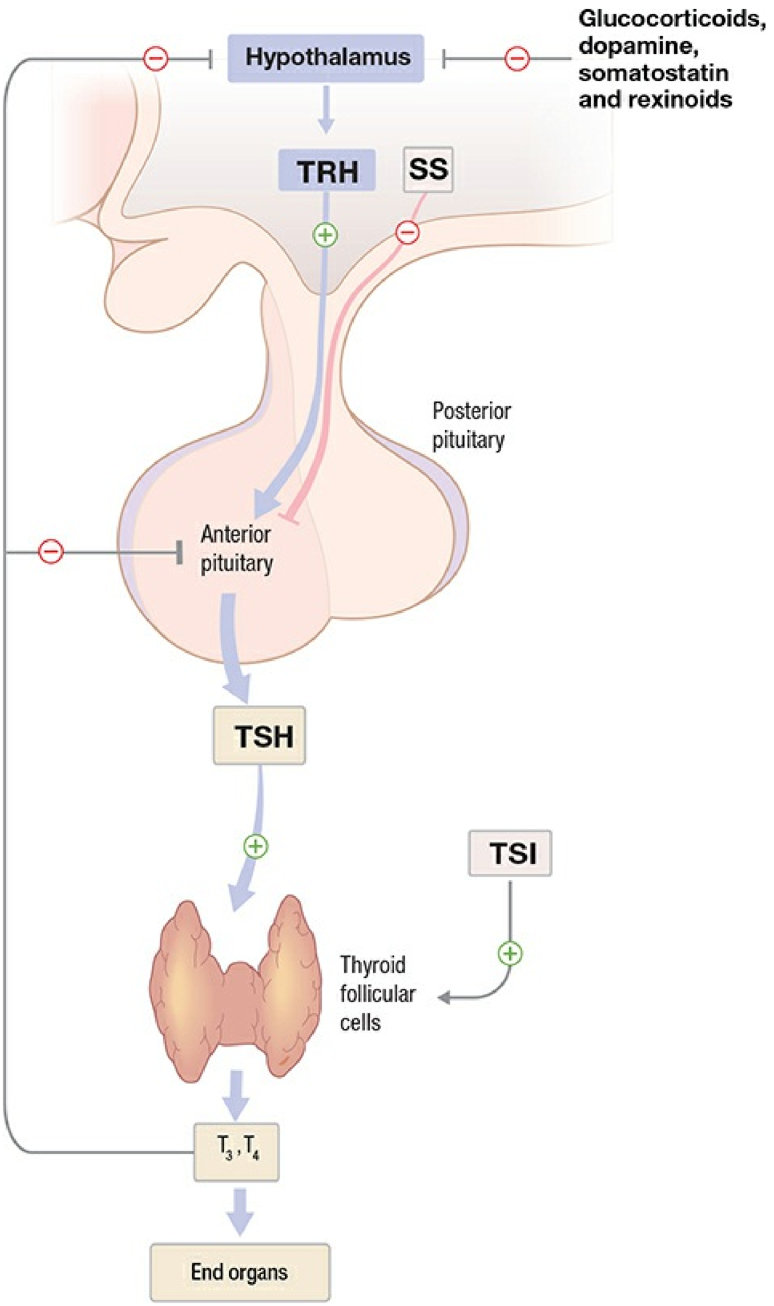

Glucocorticoids,
dopamine,
somatostatin
and rexinoids
Hypothalamus
TRH
SS
Posterior
pituitary
Anterior
pituitary
TSH
TSI
Thyroid
follicular
cells
T_3, T_4
End organs

FIGURE 2.3-4. The hypothalamic-pituitary-thyroid axis. *SS*, Somatostatin; *T_3*, triiodothyronine; *T_4*, thyroxine; *TSH*, thyroid-stimulating hormone; *TSI*, thyroid-stimulating immunoglobulin; *TRH*, thyrotropin-releasing hormone. (Reproduced with permission from USMLE-Rx.com.)

- The best initial test to screen for thyroid disease is thyroid-stimulating hormone (TSH) measurement alone. Suspicion of thyroid disease or detection of a goiter on physical exam should always prompt a check of TSH.
- If there is known history (or suspicion) of hypothalamic or pituitary disease, measuring TSH and free T_4 initially can guide more accurate assessment of thyroid function.
- Total T_4 measurement is not an adequate screening test. Ninety-nine percent of T_4 is bound to thyroxine-binding globulin (TBG). Changes in levels of TBG can occur in pregnancy, estrogen administration, and infection.
- In general, thyroid function testing should not be done in periods of acute illness, as many

factors (medications, decreased binding protein levels, transient central hypothyroidism) can alter thyroid function tests (TFTs).

TFT patterns seen in selected diseases are included in Table 2.3-5.

TABLE 2.3-5. Thyroid Function Tests in Thyroid Disease

DIAGNOSIS	TSH	T_4	T_3	CAUSES
Primary hyperthyroidism	↓	↑	↑	Graves disease, toxic multinodular goiter, toxic adenoma, amiodarone, postpartum thyrotoxicosis, postviral thyroiditis
Secondary hyperthyroidism	Normal/↑	↑	↑	Rare; caused by TSH-producing pituitary adenoma; TSH often inappropriately normal (not suppressed)
Primary hypothyroidism	↑	↓	↓	Hashimoto thyroiditis, iatrogenic (radioactive ablation, excision), drugs (lithium, amiodarone)
Secondary hypothyroidism	↓	↓	↓	Often caused by pituitary nonfunctioning macroadenomas, infiltrative diseases, or post–pituitary surgery; pituitary apoplexy (Sheehan syndrome) is a rare cause
Subclinical hypothyroidism	↑	Normal	Normal	Often with mild elevations in TSH, asymptomatic
Euthyroid sick syndrome	Normal/↓	Normal/↓	↓	Caused by any serious illness; will have ↑ reverse T_3 (nonfunctional), as T_4 is converted to rT_3 instead of T_3; thought to be protective (avoids excess catabolism in acute illness); thyroid hormone supplementation is not indicated.

A

The next best step is to add 5% dextrose to the IV fluids. In the management of DKA, it is important to start IV fluids and insulin immediately. Initially, the goal is to rehydrate the patient and ↓ blood glucose, but as blood glucose reaches 250 to 300 mg/dL, it is important to add 5% dextrose to ↓ ↓ the risk for hypoglycemia, as the anion gap acidosis is still being treated.

HYPERTHYROIDISM AND THYROTOXICOSIS

Etiologies include:

- **Graves disease:** Most common cause of hyperthyroidism. Autoimmune—TSH receptor-stimulating autoantibodies ↑ synthesis of T_3/T_4.
- **Toxic adenoma/toxic multinodular goiter:** Results in hyperthyroidism secondary to autonomous hyperactive thyroid nodules.
- **Thyroiditis:** Caused by transient inflammation of the thyroid gland with release of previously synthesized thyroid hormone; causes a temporary ↑ in circulating T_3/T_4. A hypothyroid phase may follow the hyperthyroid phase with eventual return to normal in many patients.
- **Fetal thyrotoxicosis:** Classically presents as an irritable, tachycardic infant born to a mother with Graves disease. Due to transplacental transfer of IgG TSH-stimulating antibodies.

KEY FACT

Exophthalmos, pretibial myxedema, and thyroid bruits are specific for Graves disease.

History/PE

- Patient presents with weight loss, heat intolerance, anxiety, palpitations, ↑ bowel movement frequency, myopathy/proximal muscle weakness, insomnia, and/or menstrual abnormalities.
- Physical examination can reveal warm, moist skin; goiter; hypertension; sinus tachycardia or irregular heart rhythm (atrial fibrillation, other tachyarrhythmias); fine tremor; lid lag; and hyperactive reflexes.
- Exophthalmos (direct stimulation of orbital fibroblasts by antibodies), pretibial myxedema, acropachy (soft tissue swelling of the hands) (see Fig. 2.3-5), and thyroid bruits are seen mainly in Graves disease.

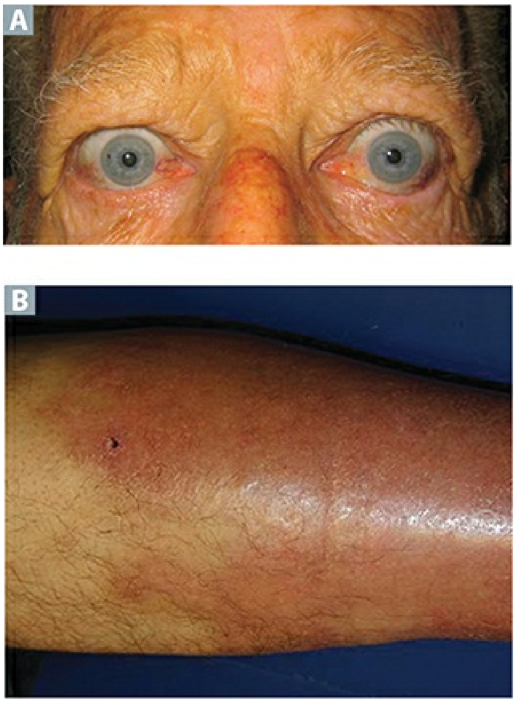


FIGURE 2.3-5. **Physical signs of Graves disease. (A)** Graves ophthalmopathy. **(B)** Pretibial myxedema. (Reproduced with permission from USMLE-Rx.com.)

- Untreated long-standing hyperthyroidism can lead to decreased bone mass.

Diagnosis

- **Best initial test:** Serum TSH level, followed by free T_4 and T_3. May need additional information provided by RAI scans and thyroglobulin levels.
- Radioactive iodine uptake (RAIU) test and scan: Measures degree and distribution of iodine uptake in the thyroid and can be used to differentiate between different causes of hyperthyroidism. Often used to differentiate functioning nodules (toxic adenomas, benign) from nonfunctioning nodules (which require biopsy for malignancy workup). See Figure 2.3-6 and Table 2.3-6.

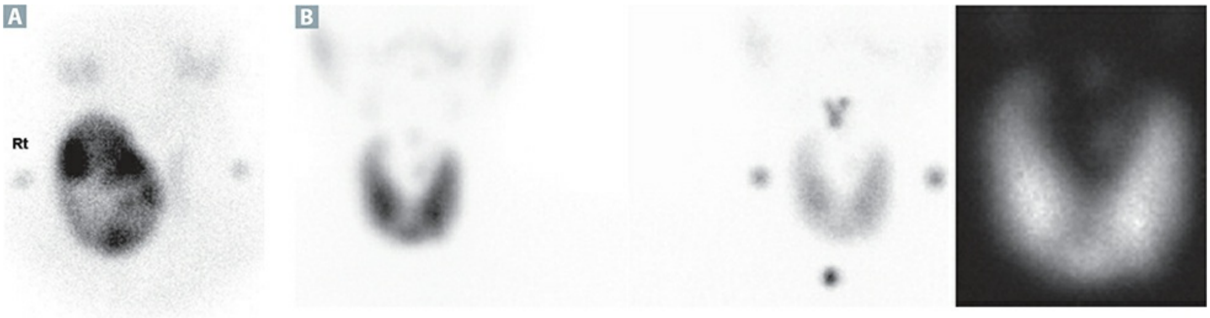


FIGURE 2.3-6. **Radioactive iodine uptake scans.** 99m-Technetium pertechnetate thyroid scans showing **(A)** multinodular areas of increased uptake and **(B)** diffuse uptake as seen in Graves disease. (Image A reproduced with permission from Cho EA, et al. A case of masked toxic adenoma in a patient with non-thyroidal illness. *BMC Endocr Disord.* 2014;14:1. Image B reproduced with permission from Coutinho E, et al. Graves' disease presenting as pseudotumor cerebri: a case report. *J Med Case Reports.* 2011;5:68.)

TABLE 2.3-6. **Diagnoses Indicated by Radioactive Iodine Findings in Hyperthyroidism**

DIAGNOSIS	RADIOACTIVE IODINE (RAI) % UPTAKE	RAI SCAN FINDINGS	THYROGLOBULIN (LEVEL IN BLOOD)
Graves disease	↑	Diffuse uptake	N/A
Multinodular goiter	Normal/↑	Multiple nodules of ↑ uptake	N/A
Toxic adenoma	Normal/↑	One area of ↑ uptake	N/A
Thyroiditis, iodine exposure, extraglandular production	↓	Low uptake	↑
Exogenous thyroid hormone	↓	Low uptake	↓

Treatment

- β-Blockade is a mainstay of treatment for hyperthyroidism, regardless of the cause. β-blockers can manage the symptoms of hyperthyroidism caused by increased adrenergic tone (tachycardia, anxiety, tremulousness).
- Antithyroid medications inhibit the oxidation of iodide, thus impairing thyroid hormone synthesis. Methimazole is the first-line agent, except during the first trimester of pregnancy, during which propylthiouracil (PTU) is preferred (methimazole is teratogenic).
- **Definitive treatment:** Radioactive I-131 thyroid ablation is generally preferred, unless there is a large, obstructive goiter or if there is Graves ophthalmopathy (which can be worsened by radioactive iodine)—the alternative to ablation is thyroidectomy.
- Administration of levothyroxine (oral T_4 replacement) prevents hypothyroidism in patients who have undergone ablation or surgery.
- Administering steroids can treat Graves ophthalmopathy if it is causing diplopia or threatening vision.

- See Table 2.3-7 for adverse drug reactions associated with antithyroid medications.

TABLE 2.3-7. Adverse Reactions and Complications for Thyrotoxicosis Treatments

DRUG/TREATMENT	ADVERSE REACTIONS AND OTHER CONSIDERATIONS
Methimazole	Rash, agranulocytosis, liver dysfunction. Contraindicated during the first trimester of pregnancy.
Propylthiouracil	Rash, arthralgias, agranulocytosis, vasculitis, liver failure (black box warning). Preferred agent in first trimester of pregnancy.
Radioactive I-131 thyroid ablation	Most common side effect is subsequent hypothyroidism (most common when treating patients with Graves disease). Contraindicated in pregnancy. Will initially worsen ophthalmopathy.
Thyroidectomy	Hypothyroidism, hypoparathyroidism, damage to nearby structures (recurrent laryngeal nerve).

- Thyroid storm is an acute, life-threatening form of thyrotoxicosis that may present with tachyarrhythmia, fever, and delirium. It can be precipitated by acute illness, iodine load, or surgery.
- Treatment of thyroid storm essentially consists of the same measures noted previously, but in rapid order. Begin with β-blockade, followed by antithyroid medication (PTU preferred in this case due to peripheral inhibition of $T_4 \rightarrow T_3$ conversion) and glucocorticoids. After administration of antithyroid medications, use of inorganic iodide (potassium iodide) blocks release and synthesis of thyroid hormone. Bile acid sequestrants (eg, cholestyramine) may be helpful, as thyroid hormone is excreted in bile and reabsorbed in the intestine.

HYPOTHYROIDISM

Most commonly caused by Hashimoto thyroiditis, but it can result from other causes (see Table 2.3-7).

- Hashimoto thyroiditis (autoimmune hypothyroidism): Associated with ⊕ antithyroglobulin and antithyroid peroxidase (anti-TPO) antibodies that precipitate thyroid destruction. Patients with Hashimoto thyroiditis have a higher risk of developing thyroid lymphoma.
- Thyroiditis (postpartum, postviral, subacute/de Quervain): Can have a hypothyroid phase that follows the hyperthyroid phase.
- Secondary hypothyroidism: Caused by pituitary tumors or pituitary surgery.
- Congenital hypothyroidism: Most common etiology is thyroid dysgenesis.
- Generalized resistance to thyroid hormone: Rare. Elevated T_3/T_4, normal to elevated TSH.

History/PE

- Hypothyroidism classically presents with weakness, fatigue, cold intolerance, constipation, weight gain, depression, hair loss, menstrual irregularities, and myopathy.
- Exam reveals dry, cold, puffy skin accompanied by edema, bradycardia, and delayed

relaxation of deep tendon reflexes.

- Congenital hypothyroidism presents with the “6 Ps”—**P**ot-bellied with a **P**rotruding umbilicus, **P**ale, **P**uffy-faced, **P**rotuberant tongue, and **P**oor brain development. Jaundice (unconjugated hyperbilirubinemia) and enlarged fontanelles can also be seen. Features of hypothyroidism arise over the first few months of life, since maternal T_4 crosses the placenta, providing somewhat adequate hormone levels at the time of birth.

Diagnosis

Best initial test: Serum TSH level, followed by free T_4 levels (see Table 2.3-5). Other common lab abnormalities include high LDL, ↑ triglycerides, ↑ creatine kinase (CK), and hyponatremia.

Treatment

- For frank hypothyroidism, administer levothyroxine. In subclinical hypothyroidism (↑ TSH, normal T_4), treat with levothyroxine if TSH >10 mU/L.
- **Myxedema coma** is a state of severe hypothyroidism that can present with ↓ mental status, hypothermia, hypotension, bradycardia, hypoglycemia, and hypoventilation. Mortality is 30% to 60%. Myxedema coma can be triggered in a hypothyroid patient by acute events such as infections, myocardial infarction (MI), stroke, trauma, sedative drugs, surgery, and medication nonadherence.
- To treat myxedema coma, admit to the intensive care unit (ICU) and urgently administer intravenous IV levothyroxine and IV hydrocortisone (unless adrenal insufficiency has already been excluded).

THYROIDITIS

Inflammation of the thyroid gland. Common subtypes include subacute granulomatous, radiation-induced, autoimmune, postpartum, infectious, and drug-induced (eg, amiodarone).

History/PE

- The subacute form presents with a tender thyroid, usually after an upper respiratory tract infection.
- All other forms are associated with painless goiter.

Diagnosis

Thyroid dysfunction (typically thyrotoxicosis followed by hypothyroidism), with ↓ uptake on RAI scan during the hyperthyroid phase.

Treatment

- Subacute thyroiditis is usually self-limited. Treatment calls for nonsteroidal anti-inflammatory drugs (NSAIDs) or oral prednisone for pain control.
- β-Blockers are appropriate for treating symptomatic hyperthyroidism. Antithyroid medications are generally not indicated. Levothyroxine is suitable for management of hypothyroidism associated with thyroiditis if TSH >10 mU/L.

Q

A 24-year-old woman with hypothyroidism presents at 10 weeks' gestation for a prenatal visit. Her only medication is levothyroxine. What adjustment is probably needed to her levothyroxine dose?

THYROID NEOPLASMS

Thyroid nodules are very common and show an ↑ incidence with age. Most (~95%) are benign.

History/PE

- Usually asymptomatic on initial presentation; discovered incidentally.
- Hyperfunctioning nodules may present with symptoms of hyperthyroidism.
- Large nodules adjacent to the trachea/esophagus may cause dysphagia, dyspnea, cough, and choking sensation.
- An ↑ risk for malignancy is associated with a history of childhood neck irradiation, "cold" nodules (minimal uptake on RAI scan), female sex, age <20 or >70, firm and fixed solitary nodules, ⊕ family history, and rapidly growing nodules with hoarseness. Hyperfunctioning ("hot") nodules are typically benign.

Diagnosis and Management

See Figure 2.3-7 for a diagnostic workup of thyroid nodules.

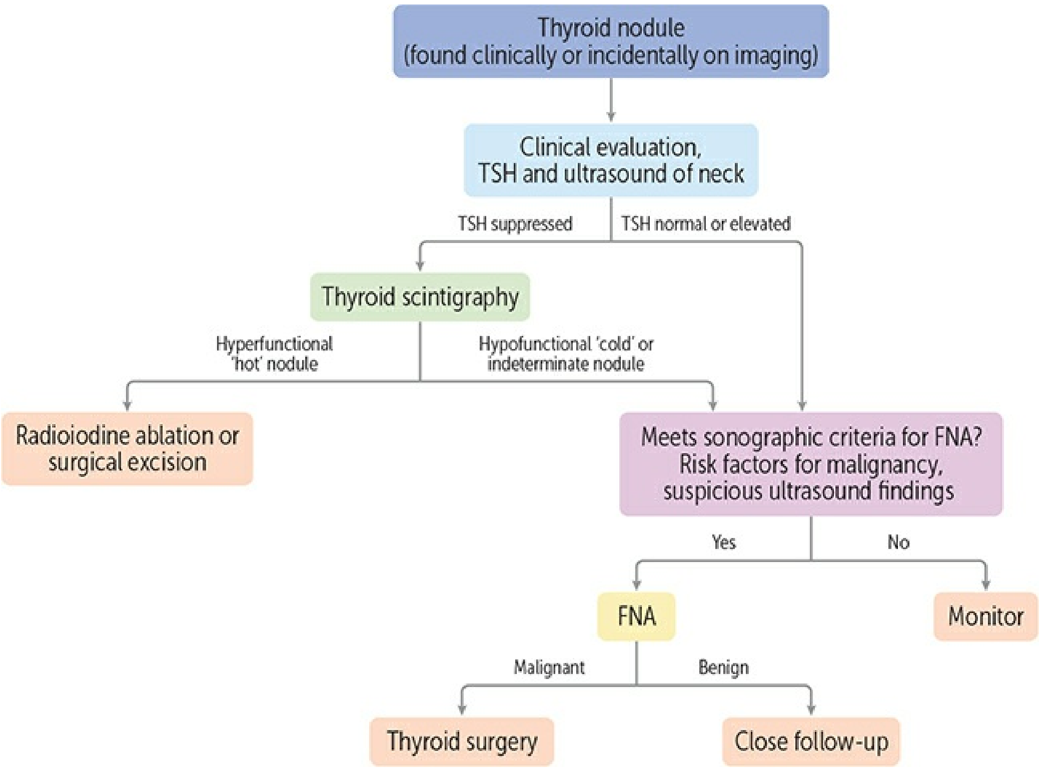

Thyroid nodule
(found clinically or incidentally on imaging)
Clinical evaluation, TSH and ultrasound of neck
TSH suppressed
TSH normal or elevated
Thyroid scintigraphy
Hyperfunctional 'hot' nodule
Hypofunctional 'cold' or indeterminate nodule
Radioiodine ablation or surgical excision
Meets sonographic criteria for FNA? Risk factors for malignancy, suspicious ultrasound findings
Yes
No
FNA
Monitor
Malignant
Benign
Thyroid surgery
Close follow-up

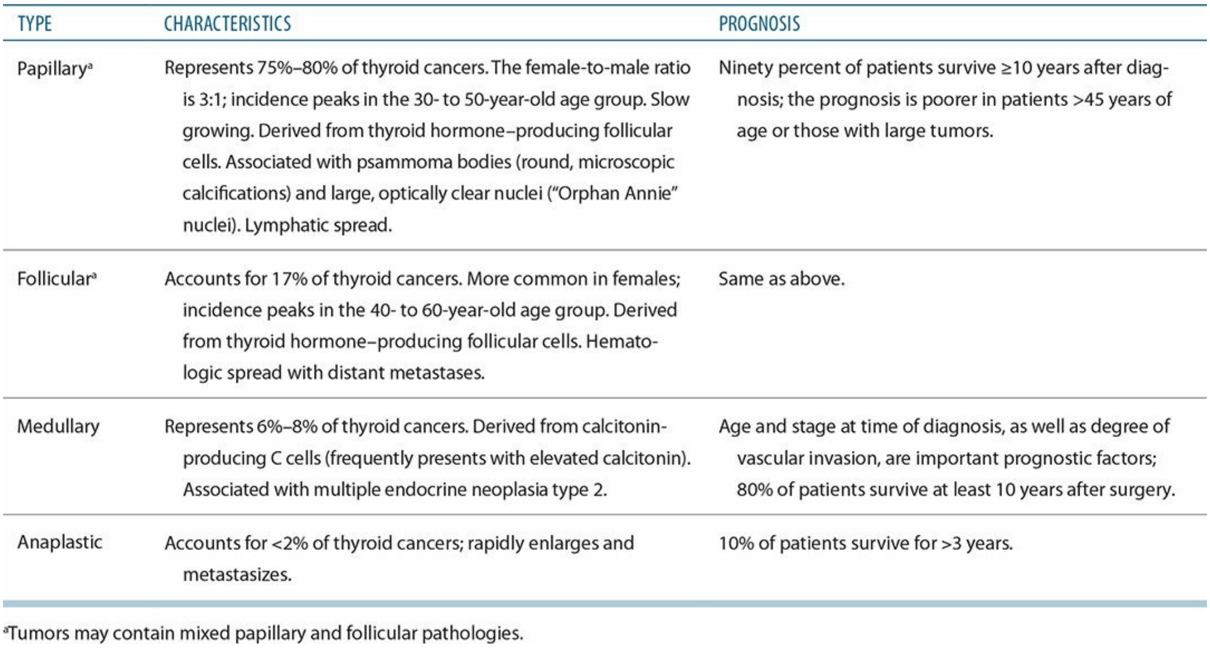
FIGURE 2.3-7. **Diagnostic steps in the workup of a thyroid nodule.** *AUS*, Atypia of undetermined significance; *FLUS*, follicular lesion of undetermined significance; *FNAC*, fine-needle aspiration cytology; *Tc*, technetium; *US*, ultrasound. (Reproduced with permission from USMLE-Rx.com.)

- **Benign nodules:** Physical exam/ultrasonography can assess for continued nodule growth or for development of suspicious characteristics (eg, microcalcifications, ↑ vascular flow, nodules that are taller than they are wide).

- **Malignant nodules:** Surgical resection with hemithyroidectomy or total thyroidectomy is best initial treatment; adjunctive radioiodine ablation following excision is appropriate for some high-risk patients.
- **Indeterminate fine-needle aspiration (FNA):** Initial management can be watchful waiting vs hemithyroidectomy (10%–30% chance of malignancy). If resected, final pathology can guide further treatment.

Table 2.3-8 summarizes the types of thyroid malignancy that can be diagnosed after biopsy.

TABLE 2.3-8. Types of Thyroid Carcinoma



TYPE	CHARACTERISTICS	PROGNOSIS
Papillary[a]	Represents 75%–80% of thyroid cancers. The female-to-male ratio is 3:1; incidence peaks in the 30- to 50-year-old age group. Slow growing. Derived from thyroid hormone–producing follicular cells. Associated with psammoma bodies (round, microscopic calcifications) and large, optically clear nuclei ("Orphan Annie" nuclei). Lymphatic spread.	Ninety percent of patients survive ≥10 years after diagnosis; the prognosis is poorer in patients >45 years of age or those with large tumors.
Follicular[a]	Accounts for 17% of thyroid cancers. More common in females; incidence peaks in the 40- to 60-year-old age group. Derived from thyroid hormone–producing follicular cells. Hematologic spread with distant metastases.	Same as above.
Medullary	Represents 6%–8% of thyroid cancers. Derived from calcitonin-producing C cells (frequently presents with elevated calcitonin). Associated with multiple endocrine neoplasia type 2.	Age and stage at time of diagnosis, as well as degree of vascular invasion, are important prognostic factors; 80% of patients survive at least 10 years after surgery.
Anaplastic	Accounts for <2% of thyroid cancers; rapidly enlarges and metastasizes.	10% of patients survive for >3 years.

[a] Tumors may contain mixed papillary and follicular pathologies.

A

The patient's dose will probably have to be ↑ (sometimes by up to 50%!). ↑ thyroxine-binding globulin (TBG) levels in pregnancy leads to ↓ free T_3/T_4 levels and ↑ TSH.

BONE AND MINERAL DISORDERS

Figure 2.3-8 reviews calcium and phosphate regulation.

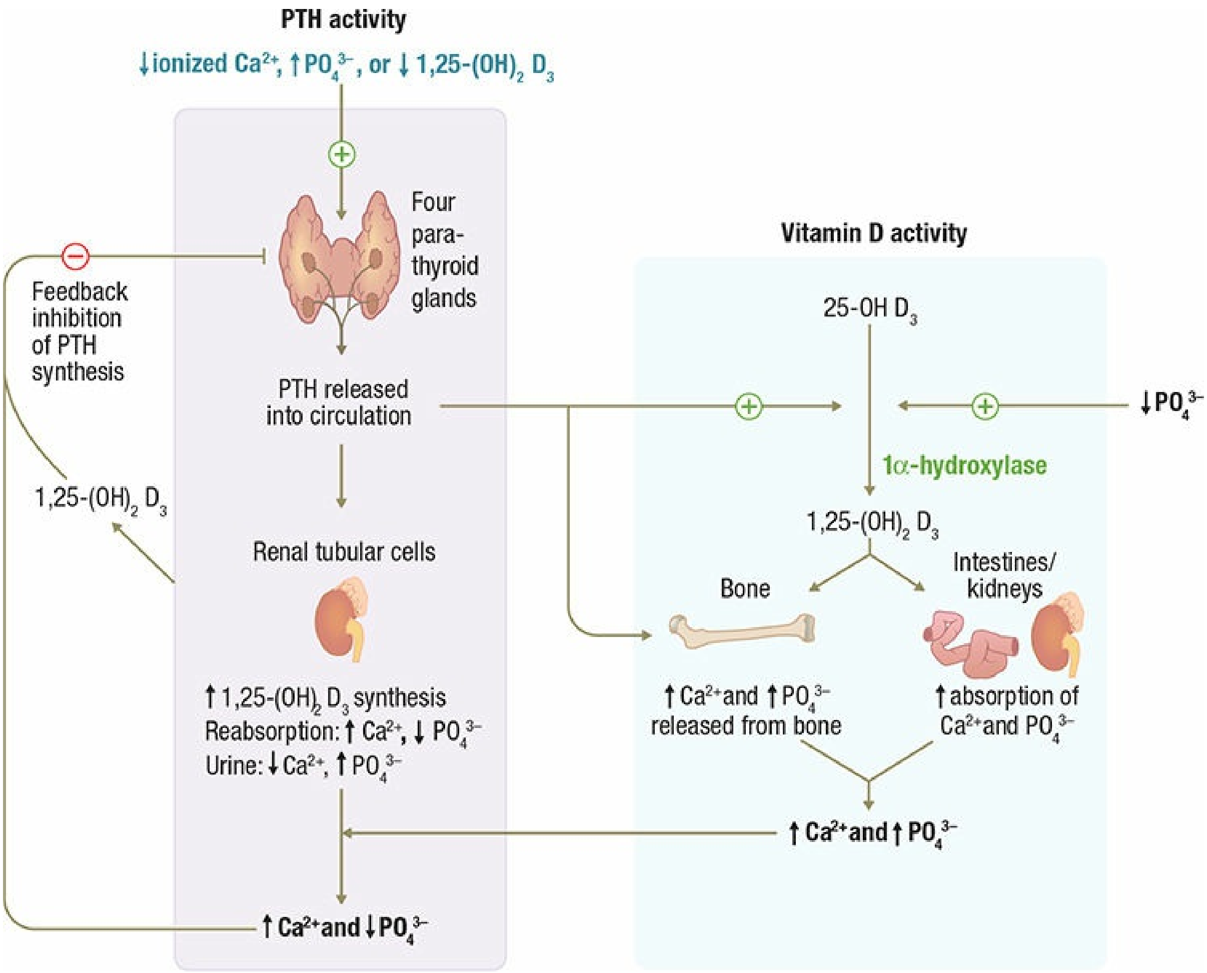

PTH activity
$\downarrow$ionized Ca^{2+}, $\uparrow PO_4^{3-}$, or $\downarrow 1,25\text{-}(OH)_2 D_3$
Four para-thyroid glands
Feedback inhibition of PTH synthesis
PTH released into circulation
$1,25\text{-}(OH)_2 D_3$
Renal tubular cells
$\uparrow 1,25\text{-}(OH)_2 D_3$ synthesis
Reabsorption: $\uparrow Ca^{2+}$, $\downarrow PO_4^{3-}$
Urine: $\downarrow Ca^{2+}$, $\uparrow PO_4^{3-}$
$\uparrow Ca^{2+}$ and $\downarrow PO_4^{3-}$
Vitamin D activity
$25\text{-}OH D_3$
$\downarrow PO_4^{3-}$
1α-hydroxylase
$1,25\text{-}(OH)_2 D_3$
Bone
Intestines/ kidneys
$\uparrow Ca^{2+}$ and $\uparrow PO_4^{3-}$ released from bone
$\uparrow$absorption of Ca^{2+} and PO_4^{3-}
$\uparrow Ca^{2+}$ and $\uparrow PO_4^{3-}$

FIGURE 2.3-8. **Overview of calcium and phosphate regulation.** *PTH,* Parathyroid hormone. (Reproduced with permission from USMLE-Rx.com)

OSTEOPOROSIS

A common metabolic bone disease characterized by low bone mass. It most often affects thin postmenopausal females, especially those of White or Asian ethnicity or descent, with risk doubling after 65 years of age. Males are also at risk for osteoporosis, but the diagnosis is often overlooked.

KEY FACT

Do not confuse osteoporosis with osteomalacia—a mineralization defect often caused by severe vitamin D deficiency that presents with bone pain, ↓ calcium/phosphate, and secondary hyperparathyroidism.

History/PE

- Osteoporosis is commonly asymptomatic even in the presence of a vertebral fracture.
- **Risk factors** include smoking, advancing age, excessive alcohol intake, a history of estrogen-depleting conditions in women (eg, amenorrhea, eating disorders, early menopause) or hypogonadism in men, physical inactivity, uncontrolled hyperthyroidism, hyperparathyroidism, chronic inflammatory disease, corticosteroid use, and Cushing syndrome.

- Exam may reveal hip fractures, vertebral compression fractures (loss of height and progressive thoracic kyphosis), and/or distal radius fractures (Colles fracture) following minimal trauma (see Fig. 2.3-9).

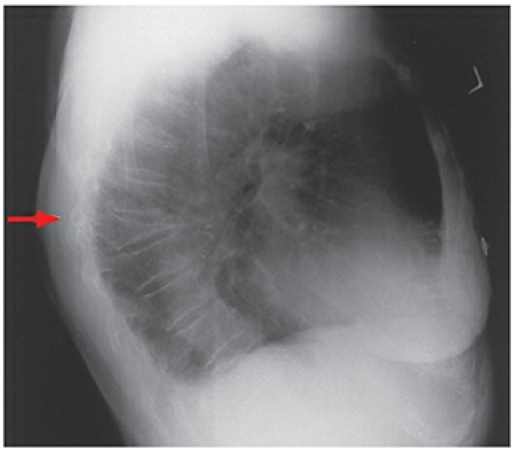


FIGURE 2.3-9. **Radiographic findings in osteoporosis.** Lateral thoracic spine radiograph shows osteoporosis and an anterior wedge deformity *(red arrow)* of a lower thoracic vertebral body with associated kyphosis. This is a typical insufficiency fracture in osteoporotic patients. (Reproduced with permission from Fauci AS, et al. *Harrison's Principles of Internal Medicine.* 17th ed. New York, NY: McGraw-Hill; 2008.)

Diagnosis

- **Diagnostic test:** Dual-energy x-ray absorptiometry (DEXA) scan is the recommended screening test for all women >65 years of age and men >70 years of age and those with other risk factors for osteoporosis.
  - **Osteoporosis:** Bone mineral density (T-score) is 2.5 standard deviations (SDs) less than normal.
  - **Osteopenia:** T-score is between 1 and 2.5 SDs below normal.
- **Lab tests:** Secondary causes reveal themselves through measurements of calcium, phosphate, parathyroid hormone (PTH), TSH, free T_4, liver enzymes, creatinine, and electrolytes. If estrogen deficiency or hypogonadism is suspected, laboratory tests should include follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and testosterone.

KEY FACT

Osteoporosis is the most common cause of pathologic fractures in women with low body weight and men >60 years of age.

Treatment

- **Lifestyle modifications:** Adequate calcium and vitamin D intake (supplementation can be used for prevention), smoking cessation, avoiding heavy alcohol use, and weight-bearing exercises.
- **Best initial treatment:** Bisphosphonates (eg, alendronate, risedronate, ibandronate, zoledronic acid) used in the treatment of osteoporosis; treatment also offered to individuals with osteopenia who have a high calculated osteoporotic fracture risk based on the FRAX calculator.

- **Other medications:** Teriparatide (PTH analogue), denosumab (a monoclonal antibody to RANK-L), and selective estrogen receptor modulators (eg, raloxifene).

Complications

Hip fracture is the most devastating consequence of low bone mineral density/osteoporosis, carrying a 50% ↑ in mortality in the year following hip fracture.

KEY FACT

Upper gastrointestinal side effects such as reflux, esophagitis, and esophageal ulcers are common reasons for oral bisphosphonate (alendronate and risedronate) intolerance.

PAGET DISEASE OF BONE

Characterized by an ↑ rate of bone turnover with both excessive resorption and formation of bone. Suspected to be caused by the effects of latent viral infection in genetically susceptible individuals. Associated with primary hyperparathyroidism and ↑ risk for osteosarcoma. The disease can affect one (monostotic) or more (polyostotic) bones, with the skull, vertebral bodies, pelvis, and long bones most commonly affected.

KEY FACT

Increased serum alkaline phosphatase with normal gamma-glutamyl transpeptidase (GGT) points to bone etiology, not liver etiology, as the cause of elevation.

History/PE

- Usually asymptomatic.
- May present with aching bone or joint pain, bony deformities, fracture at a pagetoid site, nerve entrapment, headaches, and hearing loss (latter two occur if involving the skull).

MNEMONIC

Symptoms and signs of Paget disease of bone—

PANICS

Pain
Arthralgia
Nerve compression/**N**eural deafness
Increased bone density
Cardiac failure
Skull involvement/**S**clerotic vertebra

Diagnosis

- **Best initial test:** Plain film x-rays (lytic and sclerotic lesions; see Fig. 2.3-10) usually diagnostic.

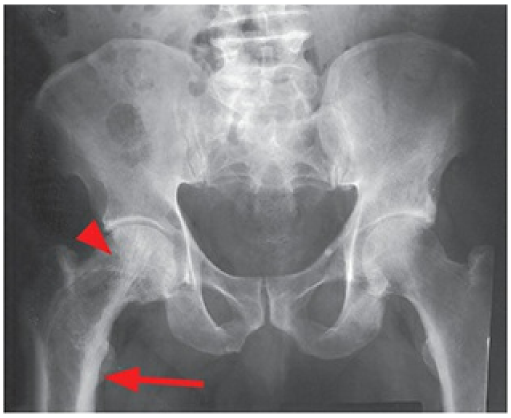


FIGURE 2.3-10. Radiographic findings in Paget disease. Pelvic radiograph demonstrates a thickened cortex *(arrow)*, thickened trabeculae *(arrowhead)*, and expansion of the right femoral head, classic signs of Paget disease. (Reproduced with permission from Fauci AS, et al. *Harrison's Principles of Internal Medicine.* 17th ed. New York, NY: McGraw-Hill; 2008.)

- Radionuclide bone scan necessary to characterize extent and sites of disease (see Fig. 2.3-11).

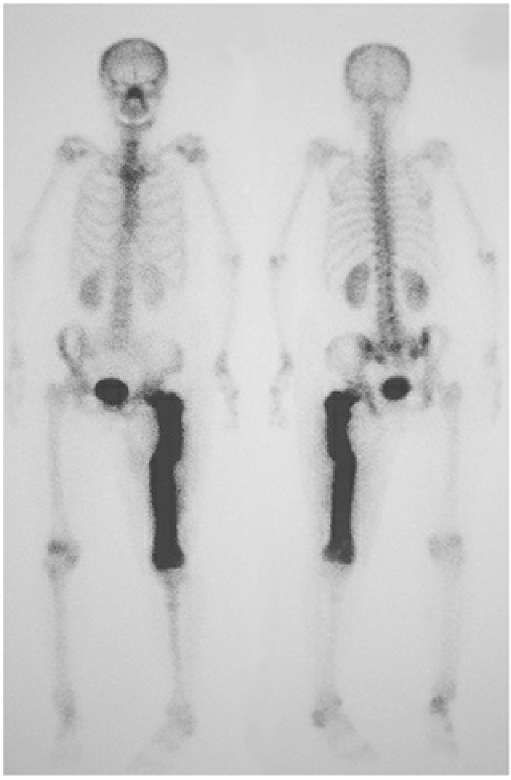


FIGURE 2.3-11. Radionuclide bone scan in Paget disease. Dark areas represent increased bone-seeking isotope uptake and depicts severe disease in the left femur. (Reproduced with permission from Takigami I, et al. Functional bracing for delayed union of a femur fracture associated with Paget's disease of the bone in an Asian patient: a case report. *J Orthop Surg Res.* 2010;5:33.)

- **Lab values:** ↑ serum alkaline phosphatase with normal calcium and phosphate levels. Must be distinguished from metastatic bone disease.

Treatment

- Most patients are asymptomatic and require no treatment.
- There is no curative treatment, but the goal is to reduce pain and disease progression.

- **Pharmacologic:** Bisphosphonates (first line), calcitonin (if intolerant to bisphosphonates), calcium and vitamin D supplementation, analgesics (NSAIDs and acetaminophen).
- **Adjunctive therapy:** Physiotherapy, occupational therapy.
- **Surgery:** If necessary, such as in the case of fractures, severe deformities, and osteoarthritis.

Complications

Osteoarthritis, pathologic fractures, high-output cardiac failure (from atrioventricular [AV] connections), and osteosarcoma (up to 1%).

KEY FACT

Bone pain and hearing loss → think Paget disease.

HYPERPARATHYROIDISM

See Figure 2.3-8 for the effects of PTH on serum calcium and phosphate regulation. For a more thorough review of hypocalcemia and hypercalcemia, see the Renal/Genitourinary chapter.

- **Primary hyperparathyroidism:** Most cases (80%) caused by a single hyperfunctioning adenoma, with the rest (15%) resulting from parathyroid hyperplasia and, rarely (5%), parathyroid carcinoma.
- **Secondary hyperparathyroidism:** A physiologic ↑ of PTH in response to renal insufficiency (caused by ↓ production of 1-25 dihydroxy vitamin D), calcium deficiency, or vitamin D deficiency.
- **Tertiary hyperparathyroidism:** Seen in patients on dialysis with long-standing secondary hyperparathyroidism, which leads to hyperplasia of the parathyroid glands. When one or more of the glands become autonomous, tertiary hyperparathyroidism results.
- **Pseudohypoparathyroidism:** PTH resistance. ↑ PTH levels but ineffective at target organs, resulting in hypocalcemia and hyperphosphatemia. Associated with Albright hereditary osteodystrophy (may have shortened fourth and fifth metatarsal or metacarpal bones).

History/PE

Most cases of primary hyperparathyroidism are asymptomatic but may show signs and symptoms of hypercalcemia (see Renal/Genitourinary chapter).

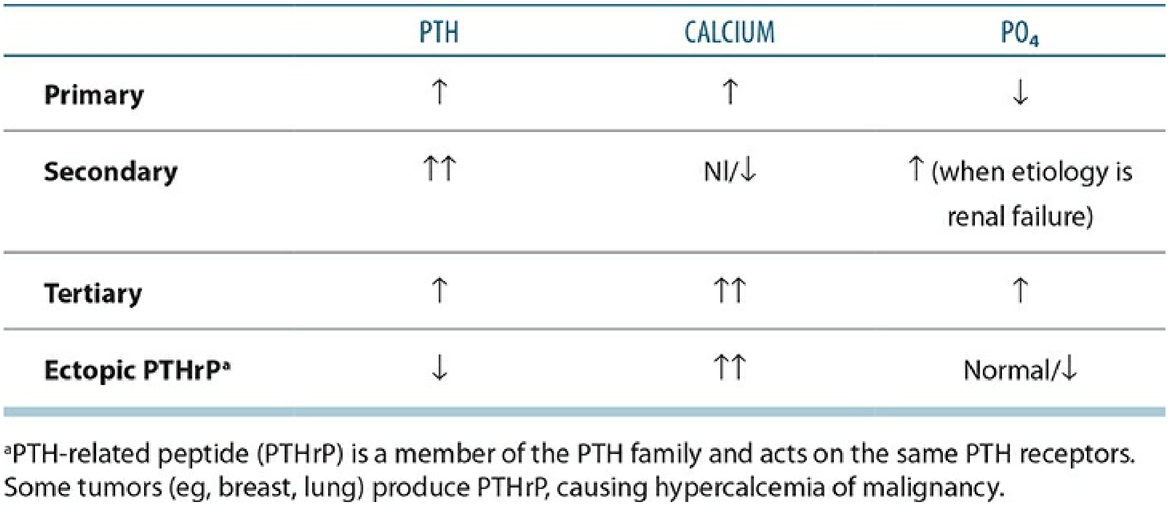
KEY FACT

Hypercalcemia is associated with “stones, bones, moans, groans, and psychiatric overtones.” Treatment: IV fluids (first-line treatment) and calcitonin. If secondary to malignancy, add bisphosphonates.

Diagnosis

- Lab results in primary hyperparathyroidism reveal hypercalcemia, hypophosphatemia, and hypercalciuria. Intact PTH is inappropriately ↑ relative to total and ionized calcium (see Table 2.3-9).

TABLE 2.3-9. **Lab Values in Hyperparathyroidism**



	PTH	CALCIUM	PO_4
Primary	↑	↑	↓
Secondary	↑↑	Nl/↓	↑ (when etiology is renal failure)
Tertiary	↑	↑↑	↑
Ectopic PTHrP[a]	↓	↑↑	Normal/↓

[a] PTH-related peptide (PTHrP) is a member of the PTH family and acts on the same PTH receptors. Some tumors (eg, breast, lung) produce PTHrP, causing hypercalcemia of malignancy.

- A 99mTc sestamibi scan, in conjunction with thyroid ultrasonography, can help localize a solitary adenoma.
- DEXA may reveal low bone mineral density or frank osteoporosis in the distal radius or other sites.
- Renal imaging can look for nephrocalcinosis and nephrolithiasis.

KEY FACT

Etiologies of hypoparathyroidism include iatrogenic (postsurgical), autoimmune, congenital (DiGeorge), and infiltrative (hemochromatosis, Wilson) diseases.

Treatment

- Best initial treatment: For acute hypercalcemia, IV fluids and calcitonin. IV bisphosphonates suitable for long-term treatment.
- Parathyroidectomy if the patient is symptomatic or if certain criteria are met (↑ ↑ calcium, ↑ creatinine, ↓ bone mineral density, <50 years of age). In the case of a solitary adenoma, 1 gland can be removed. In the setting of hyperplasia, 3.5 glands must be removed.
- In patients with chronic kidney disease, oral phosphate binders (calcium salts, sevelamer hydrochloride, and lanthanum carbonate) and restriction of dietary phosphate intake to prevent secondary hyperparathyroidism.
- Cinacalcet—a calcimimetic that acts to lower serum PTH levels—approved for use in hyperparathyroidism caused by renal failure or in patients who cannot undergo surgery.

Complications

Hypercalcemia is the most severe complication of primary hyperparathyroidism. Following parathyroidectomy, the physician should watch for hungry bone syndrome (severe and prolonged hypocalcemia caused by acute reversal of PTH and ↑ in bone uptake of calcium, phosphate, and magnesium).

KEY FACT

Hyperparathyroidism can be caused by ectopic PTH-related peptide (PTHrP) production, particularly from carcinomas of the breast, lung, and head and neck.

PITUITARY AND HYPOTHALAMIC DISORDERS

Figure 2.3-12 illustrates the hypothalamic-pituitary axis. The following sections outline the manner in which the components of this axis interact with target organs in various pathologic states.

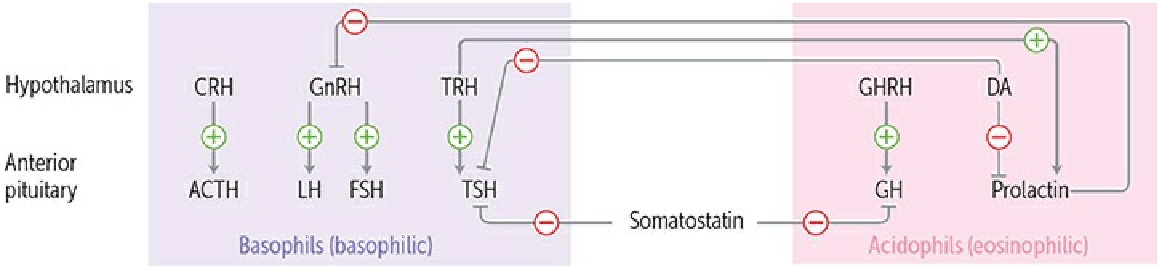


FIGURE 2.3-12. The hypothalamic-pituitary axis. *ACTH*, Adrenocorticotropic hormone; *CRH*, corticotropin-releasing hormone; *DA*, dopamine; *FSH*, follicle-stimulating hormone; *GH*, growth hormone; *GHRH*, growth hormone-releasing hormone; *GnRH*, gonadotropin-releasing hormone; *LH*, luteinizing hormone; *TRH*, thyrotropin-releasing hormone; *TSH*, thyroid-stimulating hormone. (Modified with permission from USMLE-Rx.com.)

DEFICIENCY OF PITUITARY HORMONES

Hypopituitarism is the deficiency of anterior pituitary hormones. If the posterior pituitary hormones are also affected, it is known as panhypopituitarism. Common causes include:

- Damage to pituitary gland/hypothalamus by surgery, radiation, mass lesions (tumors such as a nonfunctioning pituitary adenoma, craniopharyngioma)
- Sheehan syndrome (pituitary infarction seen in severe hemorrhage, classically in postpartum patients)
- Pituitary apoplexy (hemorrhage)
- Infiltrative disorders (hemochromatosis)
- Infections

Q

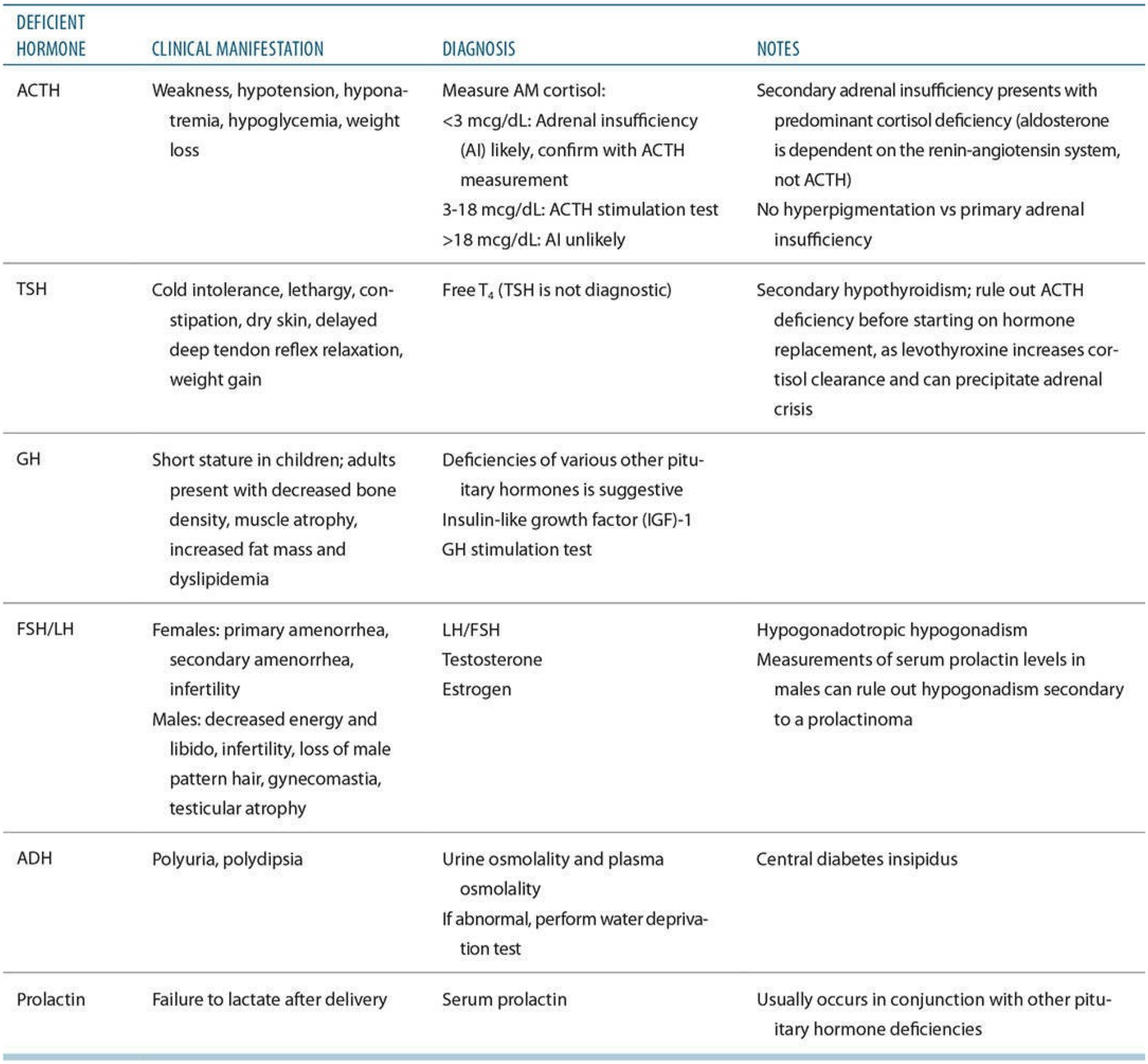
An asymptomatic 36-year-old man presents for his annual physical. Routine labs reveal a serum calcium level of 11.3 mg/dL. He returns in 2 weeks, and his serum calcium level remains elevated. Additional studies show a normal serum PTH level and a low 24-hour urinary calcium level. What is the most likely diagnosis?

Gonadotropins and growth hormone are often affected first; consequently, children first present with growth retardation, and adults present with hypogonadism. Pituitary hormone deficiencies include adrenocorticotropic hormone (ACTH) deficiency, secondary hypothyroidism, growth hormone (GH) deficiency, gonadotropin deficiency, central diabetes insipidus (DI), and prolactin deficiency.

History/PE

See Table 2.3-10 for a presentation of pituitary hormone deficiencies. Clinical manifestations may present suddenly (apoplexy, Sheehan syndrome) or gradually (radiation, infiltrative diseases).

TABLE 2.3-10. Pituitary Hormone Deficiencies



DEFICIENT HORMONE	CLINICAL MANIFESTATION	DIAGNOSIS	NOTES
ACTH	Weakness, hypotension, hyponatremia, hypoglycemia, weight loss	Measure AM cortisol: <3 mcg/dL: Adrenal insufficiency (AI) likely, confirm with ACTH measurement 3-18 mcg/dL: ACTH stimulation test >18 mcg/dL: AI unlikely	Secondary adrenal insufficiency presents with predominant cortisol deficiency (aldosterone is dependent on the renin-angiotensin system, not ACTH) No hyperpigmentation vs primary adrenal insufficiency
TSH	Cold intolerance, lethargy, constipation, dry skin, delayed deep tendon reflex relaxation, weight gain	Free T_4 (TSH is not diagnostic)	Secondary hypothyroidism; rule out ACTH deficiency before starting on hormone replacement, as levothyroxine increases cortisol clearance and can precipitate adrenal crisis
GH	Short stature in children; adults present with decreased bone density, muscle atrophy, increased fat mass and dyslipidemia	Deficiencies of various other pituitary hormones is suggestive Insulin-like growth factor (IGF)-1 GH stimulation test	
FSH/LH	Females: primary amenorrhea, secondary amenorrhea, infertility Males: decreased energy and libido, infertility, loss of male pattern hair, gynecomastia, testicular atrophy	LH/FSH Testosterone Estrogen	Hypogonadotropic hypogonadism Measurements of serum prolactin levels in males can rule out hypogonadism secondary to a prolactinoma
ADH	Polyuria, polydipsia	Urine osmolality and plasma osmolality If abnormal, perform water deprivation test	Central diabetes insipidus
Prolactin	Failure to lactate after delivery	Serum prolactin	Usually occurs in conjunction with other pituitary hormone deficiencies

Diagnosis

Routine hypopituitarism testing includes 8 am cortisol (on at least two separate occasions), free T_4 (TSH is not diagnostic), testosterone/estradiol levels, urine, and plasma osmolality. After the diagnosis of a pituitary hormone deficiency, a brain MRI can check for underlying causes. (See Table 2.3-10.)

Treatment

Hormone replacement therapy and treatment of the underlying disorder. Corresponding sections outline treatments of specific hormone deficiencies.

KEY FACT

In patients with suspected DI, check serum or urinary glucose to rule out diabetes mellitus.

DIABETES INSIPIDUS

Inability to produce concentrated urine as a result of antidiuretic hormone (ADH) dysfunction, resulting in free water loss from the kidneys. The two subtypes of diabetes insipidus (DI) are as follows:

- **Central DI (ADH deficiency):** The posterior pituitary gland fails to secrete ADH. Causes include tumor, ischemia (Sheehan syndrome), pituitary hemorrhage, traumatic brain injury, infection, metastatic disease, and autoimmune disorders (see Fig. 2.3-13).

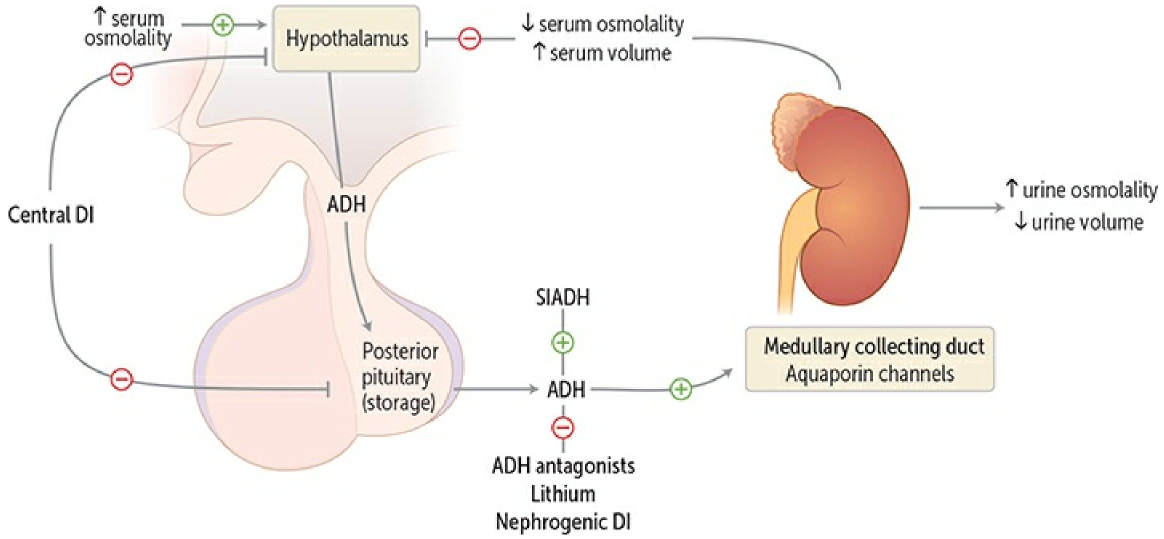

↑ serum osmolality
Hypothalamus
↓ serum osmolality
↑ serum volume
Central DI
ADH
↑ urine osmolality
↓ urine volume
SIADH
Medullary collecting duct
Aquaporin channels
Posterior pituitary (storage)
ADH
ADH antagonists
Lithium
Nephrogenic DI

FIGURE 2.3-13. **The hypothalamic-pituitary axis: Diabetes insipidus.** In central DI, ADH is not secreted from the posterior hypothalamus. In nephrogenic DI, ADH is secreted from the posterior hypothalamus, but its end-organ effects at the kidney are blocked. Both central and nephrogenic DI result in an increase in plasma osmolarity due to excessive free-water diuresis. *DI*, Diabetes insipidus; *SIADH*, syndrome of inappropriate secretion of ADH. (Reproduced with permission from USMLE-Rx.com.)

- **Nephrogenic DI (ADH resistance):** The kidneys fail to respond to circulating ADH. Causes include renal disease and drugs (eg, lithium, demeclocycline).

A

The patient most likely has familial hypocalciuric hypercalcemia (FHH), an inherited disorder caused by mutations in a calcium-sensing receptor present in the parathyroid and kidney, which presents with elevated serum calcium levels. Unlike patients with primary hyperparathyroidism, these patients are asymptomatic and have low urinary calcium levels. No treatment is required.

History/PE

- DI presents with polydipsia, polyuria, and persistent thirst with dilute urine.

- If access to water is limited (eg, in people who are institutionalized or older adults), patients may present with dehydration and severe hypernatremia, which lead to altered mental status, lethargy, seizures, and coma.

Diagnosis

- **Lab tests:** Serum osmolality > urine osmolality, ↓ urinary sodium, and possible hypernatremia.

Q

A 23-year-old man with a history of schizophrenia presents with complaints of fatigue, weakness, cramps, and headache for the past several days. He denies any other symptoms, although he had to urinate several times while in the office. Routine labs reveal hyponatremia. With water deprivation, his urine osmolality ↑. What is the most likely diagnosis?

- **Water deprivation test:** In psychogenic polydipsia and normal renal physiology, water restriction will lead to more concentrated urine. In central and nephrogenic DI, patients excrete a high volume of inappropriately dilute urine (see Fig. 2.3-14, Table 2.3-11).

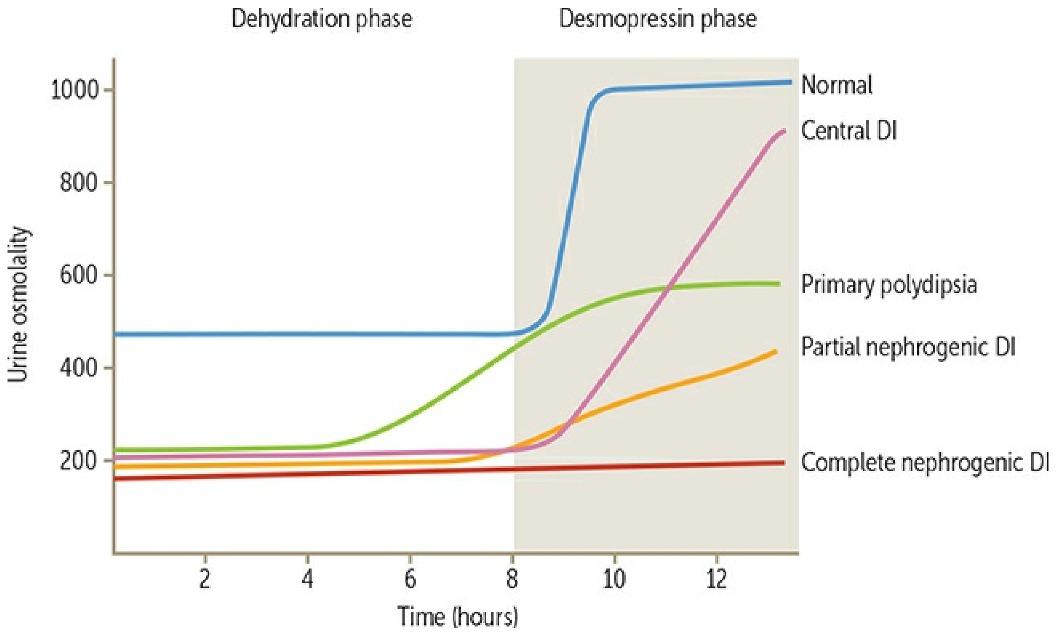
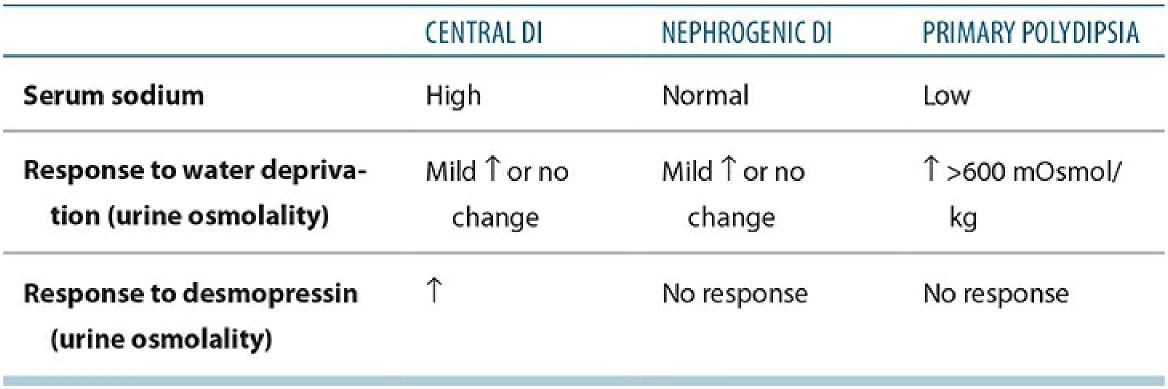


FIGURE 2.3-14. **Water deprivation test:** *DI*; Diabetes insipidus. (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.3-11. **Water Deprivation Test**



	CENTRAL DI	NEPHROGENIC DI	PRIMARY POLYDIPSIA
Serum sodium	High	Normal	Low
Response to water deprivation (urine osmolality)	Mild ↑ or no change	Mild ↑ or no change	↑ >600 mOsmol/kg
Response to desmopressin (urine osmolality)	↑	No response	No response

- **Desmopressin acetate replacement test:**
  - Also known as vasopressin, a synthetic analogue of ADH.
  - **Central DI:** ↓ urine output and ↑ urine osmolarity (by 50%–100%).
  - **Nephrogenic DI:** No effect on urine output or urine osmolarity.
- MRI may show a pituitary or hypothalamic mass in central DI.

Treatment

- Treatment of underlying cause.
- **Central DI:** Administration of desmopressin intravenously, intranasally, or orally.
- **Nephrogenic DI:** Salt restriction, hydrochlorothiazide, amiloride, low-protein diet in adults.

A

The most likely diagnosis is primary (psychogenic) polydipsia, a condition in which patients consume large volumes of hypotonic fluid, resulting in polyuria. It most often occurs in patients with psychiatric disorders. Patients present with symptoms similar to DI, but following a water deprivation test, urine osmolality ↑ (vs DI, in which urine remains dilute).

EXCESS OF PITUITARY HORMONES

Acromegaly

Elevated GH levels in adults, most commonly caused by a benign pituitary GH-secreting adenoma (see Fig. 2.3-15). Children with excess GH production present with gigantism.

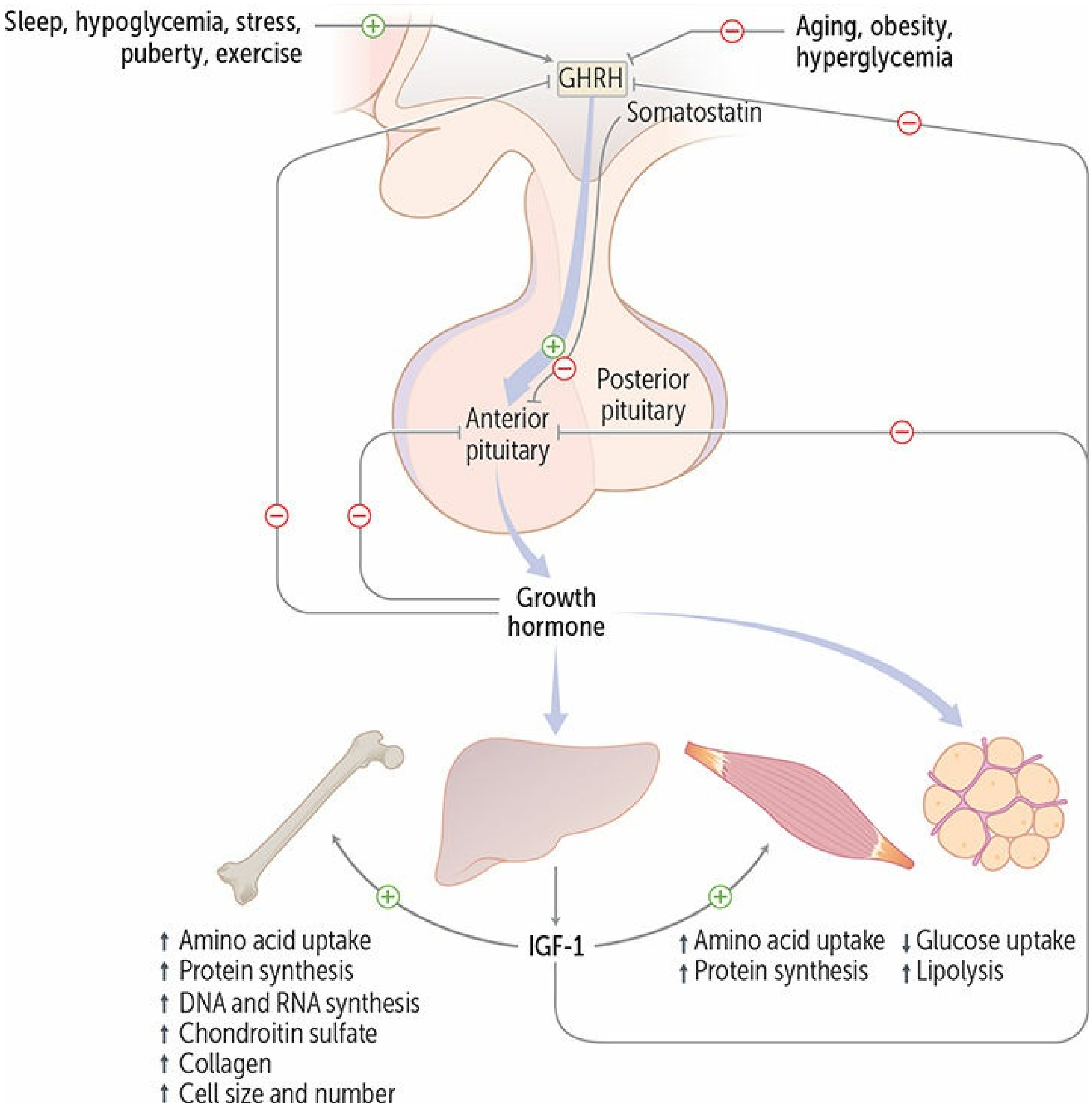

Sleep, hypoglycemia, stress, puberty, exercise
+
GHRH
−
Aging, obesity, hyperglycemia
Somatostatin
−
+
−
Posterior pituitary
Anterior pituitary
−
−
−
Growth hormone
+
+
IGF-1
↑ Amino acid uptake
↑ Protein synthesis
↑ DNA and RNA synthesis
↑ Chondroitin sulfate
↑ Collagen
↑ Cell size and number
↑ Amino acid uptake
↑ Protein synthesis
↓ Glucose uptake
↑ Lipolysis

FIGURE 2.3-15. **The hypothalamic–anterior pituitary axis (hypophyseal portal system): acromegaly.** GHRH, Growth hormone-releasing hormone; IGF-1, insulin-like growth factor 1. (Reproduced with permission from USMLE-Rx.com.)

History/PE

- Pituitary adenoma may cause headache, cranial nerve defects, and bitemporal hemianopsia due to compression of the optic chiasm.
- Systemic manifestations include:
  - Increased skeletal and soft tissue growth manifesting as enlargement of the skull (frontal bossing, wide-spaced teeth) and hands and feet, malocclusion of the jaw, coarsening of facial features, and carpal tunnel syndrome
  - Degeneration of cartilage resembling osteoarthritis
  - Skin thickening and skin tags
  - Hyperhidrosis
  - Organomegaly (eg, tongue enlargement)
- Associated with an increased risk for:
  - Obstructive sleep apnea

  - Cardiovascular abnormalities such as hypertension, left ventricular hypertrophy, and cardiomyopathy with diastolic dysfunction (most common cause of death)
  - Type 2 DM
  - Diverticulosis
  - Colon cancer

Diagnosis

- **Lab tests:** Levels of IGF-1 increase with acromegaly; diagnosis can be confirmed with an oral glucose suppression test (GH levels will remain elevated despite glucose administration). Baseline GH is not a reliable test, as GH levels fluctuate widely throughout the day (see Fig. 2.3-16).

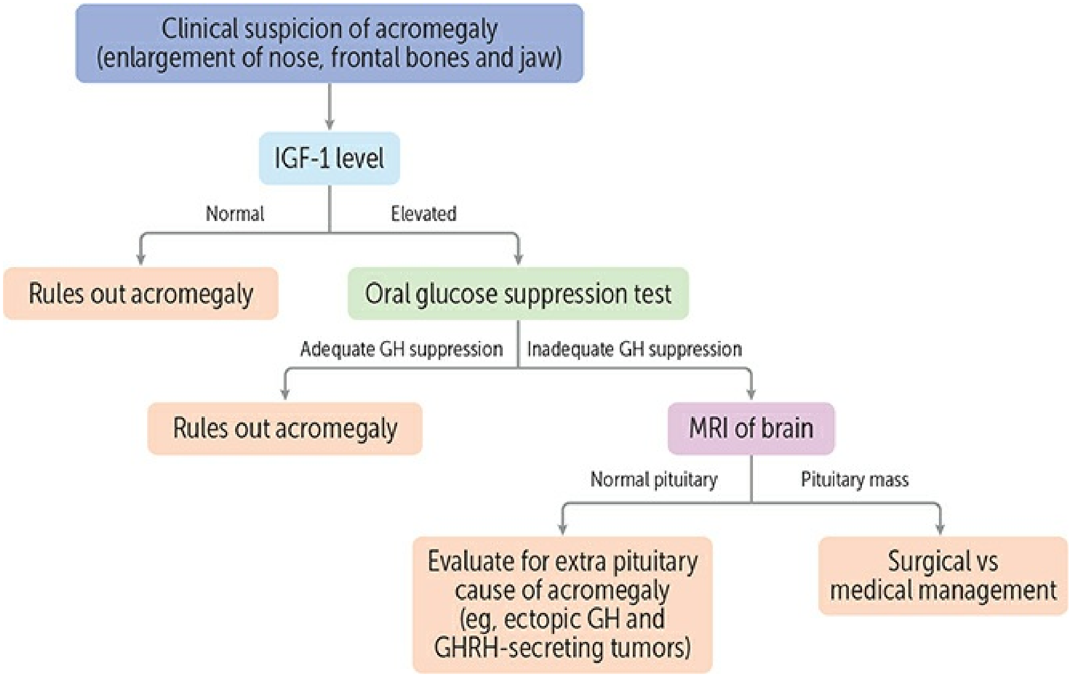

Clinical suspicion of acromegaly (enlargement of nose, frontal bones and jaw)
IGF-1 level
Normal
Elevated
Rules out acromegaly
Oral glucose suppression test
Adequate GH suppression
Inadequate GH suppression
Rules out acromegaly
MRI of brain
Normal pituitary
Pituitary mass
Evaluate for extra pituitary cause of acromegaly (eg, ectopic GH and GHRH-secreting tumors)
Surgical vs medical management

FIGURE 2.3-16. **Diagnostic algorithm for acromegaly.** *GH*, Growth hormone; *GHRH*, growth hormone-releasing hormone; *IGF-1*, insulin-like growth factor 1. (Reproduced with permission from USMLE-Rx.com.)

- **Imaging:** MRI shows a sellar lesion.

Treatment

- **Surgery:** Trans-sphenoidal surgical resection.
- **Medical therapy:** Octreotide or lanreotide (somatostatin analogues) to suppress GH secretion; pegvisomant (a GH receptor antagonist) to block the peripheral actions of GH.
- **Radiation:** Effective when surgical and medical therapies fail.

KEY FACT

Measurement of IGF-1 levels—not GH levels—can confirm acromegaly!

HYPERPROLACTINEMIA

Hyperprolactinemia refers to elevated prolactin levels, most commonly caused by a pituitary adenoma (see Fig. 2.3-17). Prolactinoma is the most common functioning pituitary tumor. Other causes include physiologic ones (pregnancy, lactation); pituitary stalk compression from other masses (eg, craniopharyngioma, meningioma, nonsecreting pituitary tumor); hypothalamic dysfunction; drugs (eg, dopamine antagonists, selective serotonin reuptake inhibitors [SSRIs]); and systemic conditions such as renal failure, cirrhosis, and hypothyroidism.

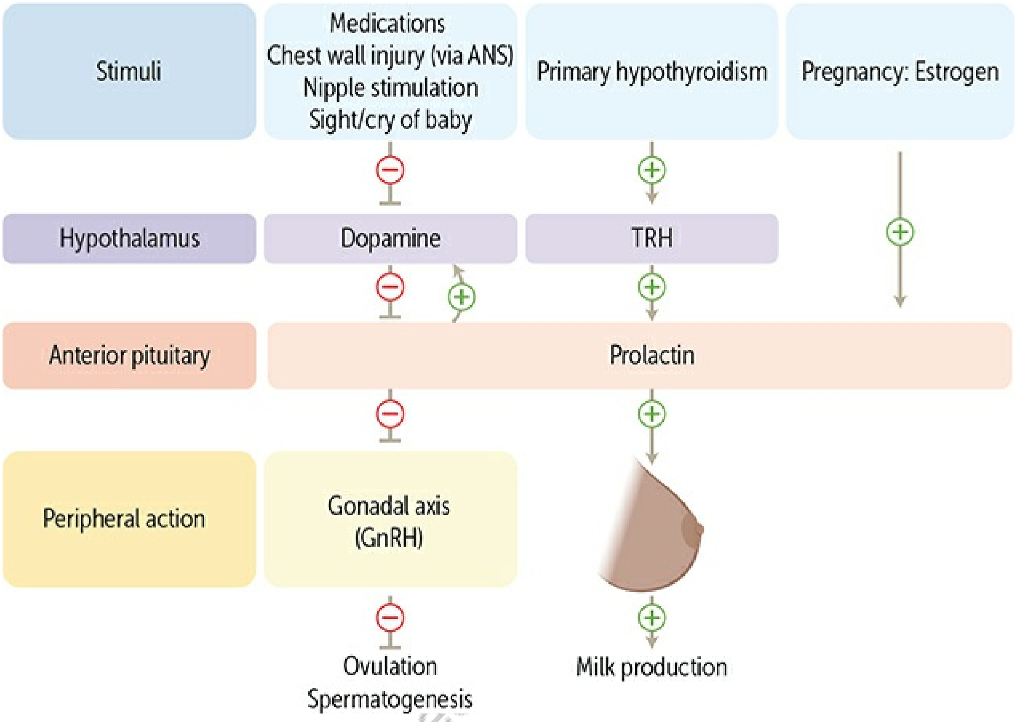

Stimuli
Medications
Chest wall injury (via ANS)
Nipple stimulation
Sight/cry of baby
Primary hypothyroidism
Pregnancy: Estrogen
Hypothalamus
Dopamine
TRH
Anterior pituitary
Prolactin
Peripheral action
Gonadal axis
(GnRH)
Ovulation
Spermatogenesis
Milk production

FIGURE 2.3-17. **The hypothalamic–anterior pituitary axis (hypophyseal portal system): Prolactin regulation.** *ANS*, Autonomic nervous system; *FSH*, follicle-stimulating hormone; *GnRH*, gonadotropin-releasing hormone; *LH*, luteinizing hormone; *TRH*, thyrotropin-releasing hormone. (Reproduced with permission from USMLE-Rx.com.)

History/PE

Elevated prolactin inhibits GnRH secretion and consequently lowers LH and FSH secretion, manifesting as infertility, galactorrhea, gynecomastia, impotence, and amenorrhea. Bitemporal hemianopsia may also be present.

KEY FACT

Rule out pregnancy in all cases of hyperprolactinemia!

Diagnosis

- Serum prolactin level is typically >200 ng/mL.
- Pregnancy test to exclude pregnancy.
- MRI shows a sellar lesion.

Treatment

- **Best initial treatment:** Dopamine agonists (eg, cabergoline, bromocriptine).

- **Trans-sphenoidal surgery:** Indicated in adenomas refractory to medical management or with compressive effects (eg, visual loss).
- **Radiation:** Rarely indicated.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a common cause of euvolemic hyponatremia that results from persistent ADH release independent of serum osmolality.

History/PE

May be associated with central nervous system (CNS) disease (eg, head injury, tumor), pulmonary disease (eg, sarcoid, chronic obstructive pulmonary disease [COPD], pneumonia), ectopic tumor production/paraneoplastic syndrome (eg, small cell lung carcinoma), and drugs (eg, antipsychotics, antidepressants, NSAIDs). Euvolemic on physical exam.

Diagnosis

- Serum osmolality <280 mOsm/kg (hypotonic)
- Urine osmolality >100 mOsm/kg in the setting of serum hypo-osmolarity without a physiologic reason for ↑ ADH (eg, congestive heart failure, cirrhosis, hypovolemia)
- Urinary sodium level often ≥40 mEq/L

Treatment

- Exploration of and addressing the underlying cause
- **Best initial treatment:** Restriction of fluid
- **Persistent or symptomatic hyponatremia (<120 mEq/L):** IV hypertonic saline therapy
- **Severe SIADH:** ADH antagonists (eg, tolvaptan, conivaptan)
- **Chronic SIADH:** Demeclocycline

KEY FACT

Fluid restriction is the cornerstone of SIADH treatment. Hyponatremia should be corrected slowly to prevent osmotic demyelination syndrome.

ADRENAL GLAND DISORDERS

See Figure 2.3-18 for an overview of adrenal anatomy, regulatory control, and secretory products.

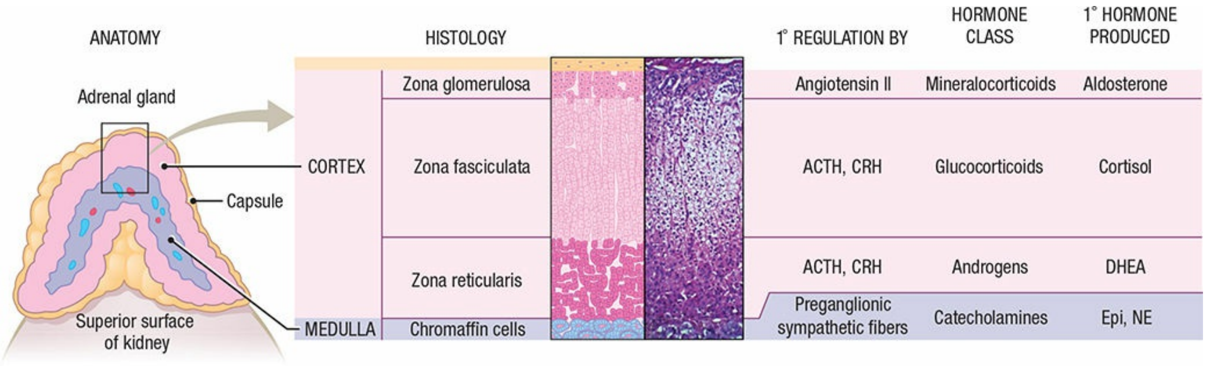

ANATOMY
HISTOLOGY
1° REGULATION BY
HORMONE CLASS
1° HORMONE PRODUCED
Adrenal gland
Capsule
Superior surface of kidney
CORTEX
MEDULLA
Zona glomerulosa
Zona fasciculata
Zona reticularis
Chromaffin cells
Angiotensin II
Mineralocorticoids
Aldosterone
ACTH, CRH
Glucocorticoids
Cortisol
ACTH, CRH
Androgens
DHEA
Preganglionic sympathetic fibers
Catecholamines
Epi, NE

FIGURE 2.3-18. Overview of adrenal anatomy, regulatory control, and secretory products. *ACTH*, Adrenocorticotropic hormone; *CRH*, corticotropin-releasing hormone; *DHEA*, dehydroepiandrosterone; *Epi*, epinephrine; *NE*, norepinephrine. (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

Dehydroepiandrosterone sulfate (DHEAS) is produced only by the adrenal gland.

ADRENAL INSUFFICIENCY

Manifested by an inadequate production of adrenal hormones, including glucocorticoids and/or mineralocorticoids, AI may be primary, secondary, or tertiary. Etiologies are as follows:

- **Primary:** In the United States, most commonly caused by **autoimmune** adrenal cortical destruction (Addison disease). Other causes include infections (tuberculosis [TB], HIV, histoplasmosis), congenital enzyme deficiencies, and adrenal hemorrhage (Waterhouse-Friderichsen syndrome from Neisseria meningitidis).
- **Secondary/tertiary:** Caused by ↓ ACTH production by the pituitary gland (secondary) or ↓ CRH corticotropin-releasing hormone production by the hypothalamus (tertiary); most often caused by cessation of long-term glucocorticoid treatment (often with higher doses and longer duration of therapy).

KEY FACT

Primary AI is associated with ↑ skin pigmentation, ↓ glucocorticoids, and ↓ mineralocorticoids. Secondary AI is only associated with ↓ glucocorticoids and does not have skin pigmentation or hyperkalemia.

History/PE

- Most symptoms are nonspecific.
- Common concerns include weakness, fatigue, anorexia with weight loss, and GI complaints (eg, nausea, abdominal pain).
- Hyperpigmentation (caused by ↑ ACTH secretion) and non–anion gap metabolic acidosis (caused by ↓ aldosterone) occur in primary AI. Hyperpigmentation is not seen in secondary or tertiary AI due to a decrease in ACTH secretion.
- Hypotension, confusion, and coma are seen in acute adrenal crisis (eg, stopping long-term

steroids).

MNEMONIC

The 4 S's of adrenal crisis management—

Salt: 0.9% saline
Steroids: IV hydrocortisone
Support (hemodynamic, glucose)
Search for the underlying illness

Diagnosis

- Lab tests: Hypoglycemia, electrolyte imbalances (see Table 2.3-12).

TABLE 2.3-12. **Laboratory Findings in Adrenal Insufficiency**

	CORTISOL	ALDOSTERONE	ACTH	SODIUM	POTASSIUM
Primary adrenal insufficiency	↓	↓	↑	↓	↑↑
Secondary/ tertiary adrenal insufficiency	↓	Normal	↓	Normal/↓	Nl

- 8 AM plasma cortisol levels and ACTH levels (see Table 2.3-12, Fig. 2.3-19). An 8 AM plasma cortisol level <3 μg/dL in the absence of exogenous glucocorticoid administration is diagnostic of AI.

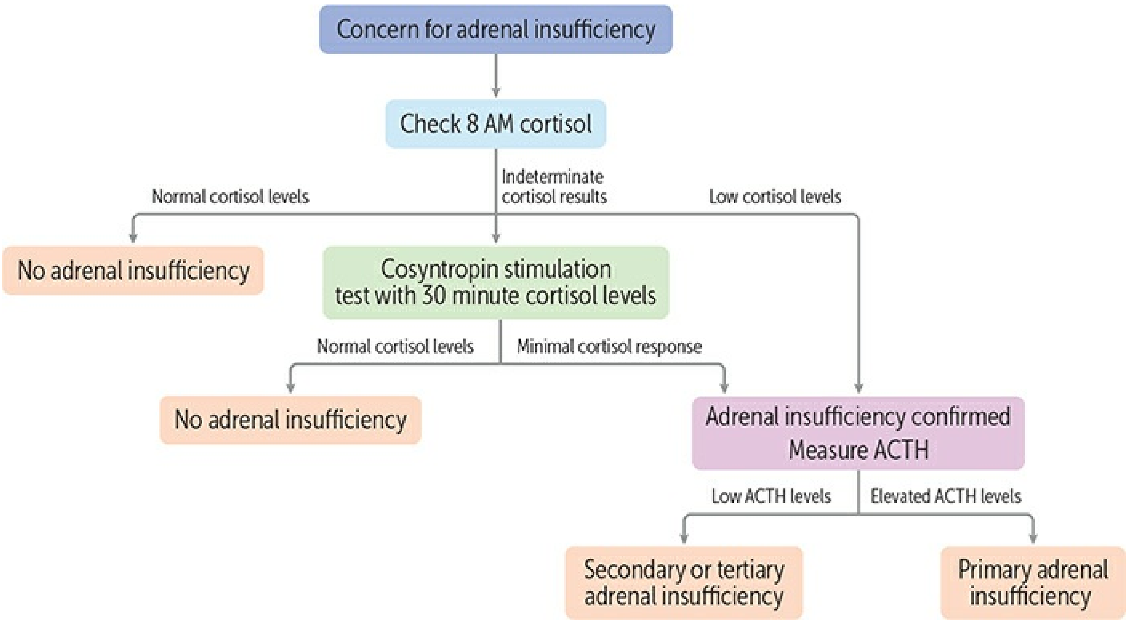

Concern for adrenal insufficiency
Check 8 AM cortisol
Normal cortisol levels
Indeterminate cortisol results
Low cortisol levels
No adrenal insufficiency
Cosyntropin stimulation test with 30 minute cortisol levels
Normal cortisol levels
Minimal cortisol response
No adrenal insufficiency
Adrenal insufficiency confirmed Measure ACTH
Low ACTH levels
Elevated ACTH levels
Secondary or tertiary adrenal insufficiency
Primary adrenal insufficiency

FIGURE 2.3-19. **Diagnostic algorithm for adrenal insufficiency.** (Modified with permission from USMLE-Rx.com.)

- If morning cortisol levels are nondiagnostic, the test of choice is synthetic ACTH stimulation (cosyntropin) test. Failure of cortisol to rise >20 μg/dL following ACTH administration confirms the diagnosis.

KEY FACT

Do not delay the administration of steroids for diagnostic testing in a patient with suspected AI.

Treatment

- **Primary:** Glucocorticoid and mineralocorticoid replacement
- **Secondary/tertiary:** Only glucocorticoid replacement necessary (mineralocorticoid production is not ACTH dependent)
- **Acute adrenal crisis:** IV steroids, correction of electrolyte abnormalities, 50% dextrose to correct hypoglycemia, and initiation of aggressive volume resuscitation

Prevention

- ↑ steroids during periods of stress (eg, major surgery, trauma, infection).
- In patients on chronic steroid therapy, taper slowly to prevent secondary/tertiary AI.

PHEOCHROMOCYTOMA

A tumor of chromaffin tissue that secretes catecholamines and is found either in the adrenal medulla or in extra-adrenal sites. Most commonly associated with multiple endocrine neoplasia type 2A (MEN2A) and MEN type 2B (MEN2B).

MNEMONIC

Pheochromocytoma rule of 10's—

10% Extra-adrenal
10% Bilateral
10% Malignant
10% Occur in children
>25% Familial (adults)

History/PE

- Pheochromocytoma presents with paroxysmal tachycardia, palpitations, chest pain, diaphoresis, episodic or persistent hypertension, headache, tremor, anxiety, pallor, and weight loss. It may be misdiagnosed as anxiety/panic disorder.
- Obtaining a family history can rule out genetic causes of pheochromocytoma (eg, MEN2A/2B, von Hippel–Lindau disease, neurofibromatosis type 1).

Diagnosis

- **Best initial test:** Indicated by ↑ 24-hour urine metanephrines and catecholamines or plasma-fractionated metanephrines.

- **Helpful labs:** Hyperglycemia ± polycythemia (if EPO secreted).
- **Imaging (only after labs):** CT or MRI of adrenal glands (see Fig. 2.3-20). A nuclear metaiodobenzylguanidine (MIBG) scan can localize extra-adrenal lesions and metastatic disease.

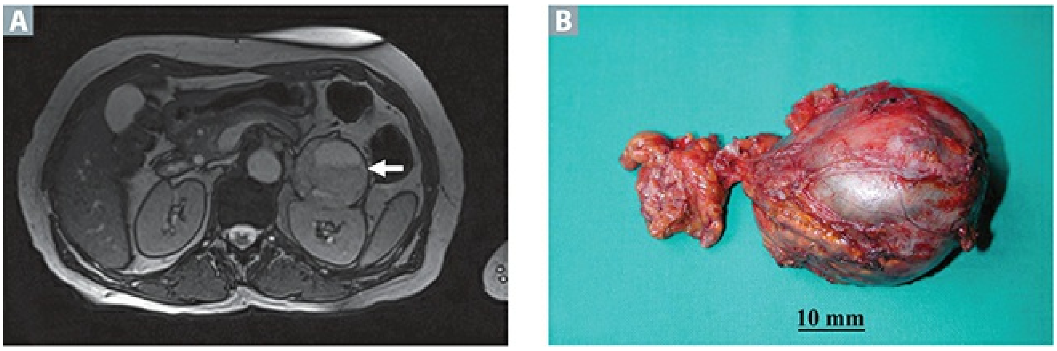


FIGURE 2.3-20. **Pheochromocytoma. (A)** MRI showing left suprarenal mass *(arrow)*. **(B)** Pheochromocytoma postsurgical resection. (Reproduced with permission from Roghi A, et al. Adrenergic myocarditis in pheochromocytoma. *J Cardiovasc Magn Reson.* 2011;13:4.)

MNEMONIC

The 5 Ps of pheochromocytoma—

Pressure (BP)
Pain (headache)
Perspiration
Palpitations
Pallor

Treatment

- Surgical resection.
- Preoperatively, first α-adrenergic blockade (phenoxybenzamine) to control hypertension, followed by β-blockade to control tachycardia. β-Blockade should never be given first, as unopposed α-adrenergic–mediated vasoconstriction can lead to severe hypertension.
- If bilateral adrenalectomy, glucocorticoids to prevent acute adrenal insufficiency.

KEY FACT

In pheochromocytoma, administration of α-blockers should occur before β-blockers to prevent hypertensive crisis.

CUSHING SYNDROME

Cushing syndrome is caused by elevated serum cortisol levels, and it most frequently develops secondary to prolonged treatment with exogenous corticosteroids. The most common endogenous cause is hypersecretion of ACTH from a pituitary adenoma (known as *Cushing disease;* see Fig. 2.3-21). Other endogenous causes include excess adrenal secretion of cortisol (eg, bilateral adrenal hyperplasia, adrenal adenoma, adrenal cancer) and ectopic

ACTH production from an occult neoplasm (eg, carcinoid tumor, medullary thyroid cancer, small cell lung cancer).

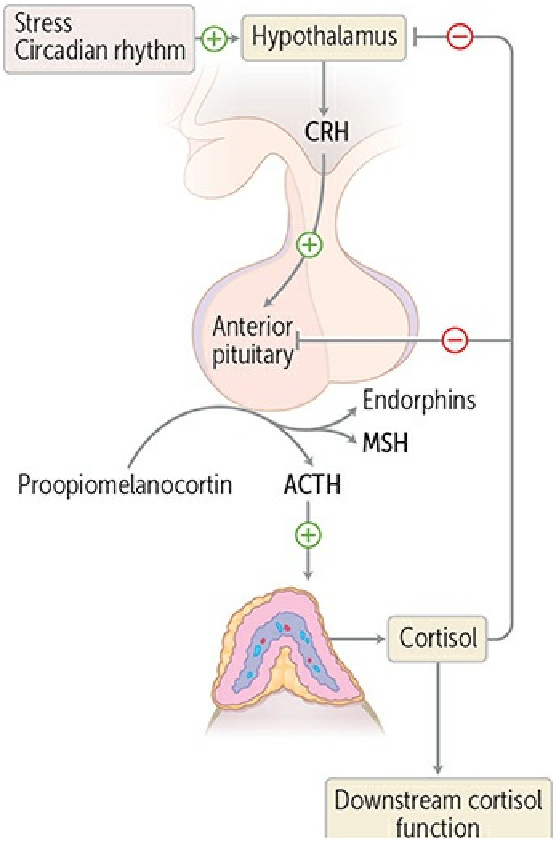

Stress
Circadian rhythm
+
Hypothalamus
−
CRH
+
Anterior pituitary
−
Endorphins
MSH
Proopiomelanocortin
ACTH
+
Cortisol
Downstream cortisol function

FIGURE 2.3-21. **The hypothalamic-anterior pituitary axis (hypophyseal portal system): Cushing disease.** *ACTH*, Adrenocorticotropic hormone; *CRH*, corticotropin-releasing hormone; *MSH*, melanocyte-stimulating hormone. (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

Cushing syndrome: Too much cortisol.
Cushing disease: Too much cortisol from an ACTH-producing pituitary adenoma.

History/PE

See Figure 2.3-22 for classic signs and symptoms of Cushing syndrome.

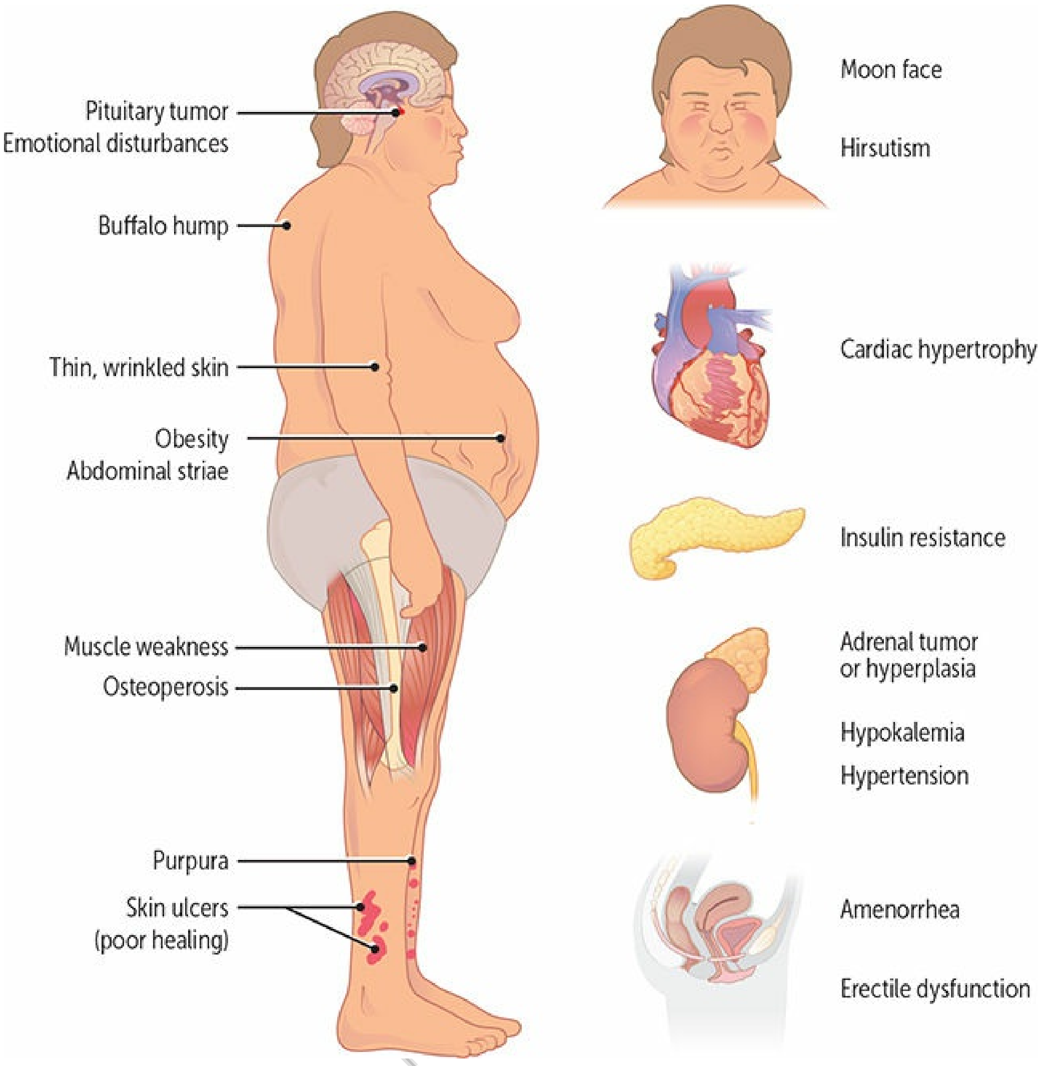

Pituitary tumor
Emotional disturbances
Buffalo hump
Thin, wrinkled skin
Obesity
Abdominal striae
Muscle weakness
Osteoporosis
Purpura
Skin ulcers
(poor healing)
Moon face
Hirsutism
Cardiac hypertrophy
Insulin resistance
Adrenal tumor
or hyperplasia
Hypokalemia
Hypertension
Amenorrhea
Erectile dysfunction

FIGURE 2.3-22. **Physical findings in Cushing syndrome.** (Modified with permission from USMLE-Rx.com.)

MNEMONIC

Cushing syndrome symptoms—

CUSHINGOID

Cataracts
Ulcers
Skin (striae, bruising, thinning, ulcer)
Hirsutism, hypertension
Infections
Necrosis (femur head)
Glycosuria
Obesity, osteoporosis
Immunosuppression
Diabetes

Diagnosis

See Figure 2.3-23 for the diagnostic algorithm. Table 2.3-13 outlines important lab findings that aid in diagnosis. Diagnosis follows a stepwise progression of tests.

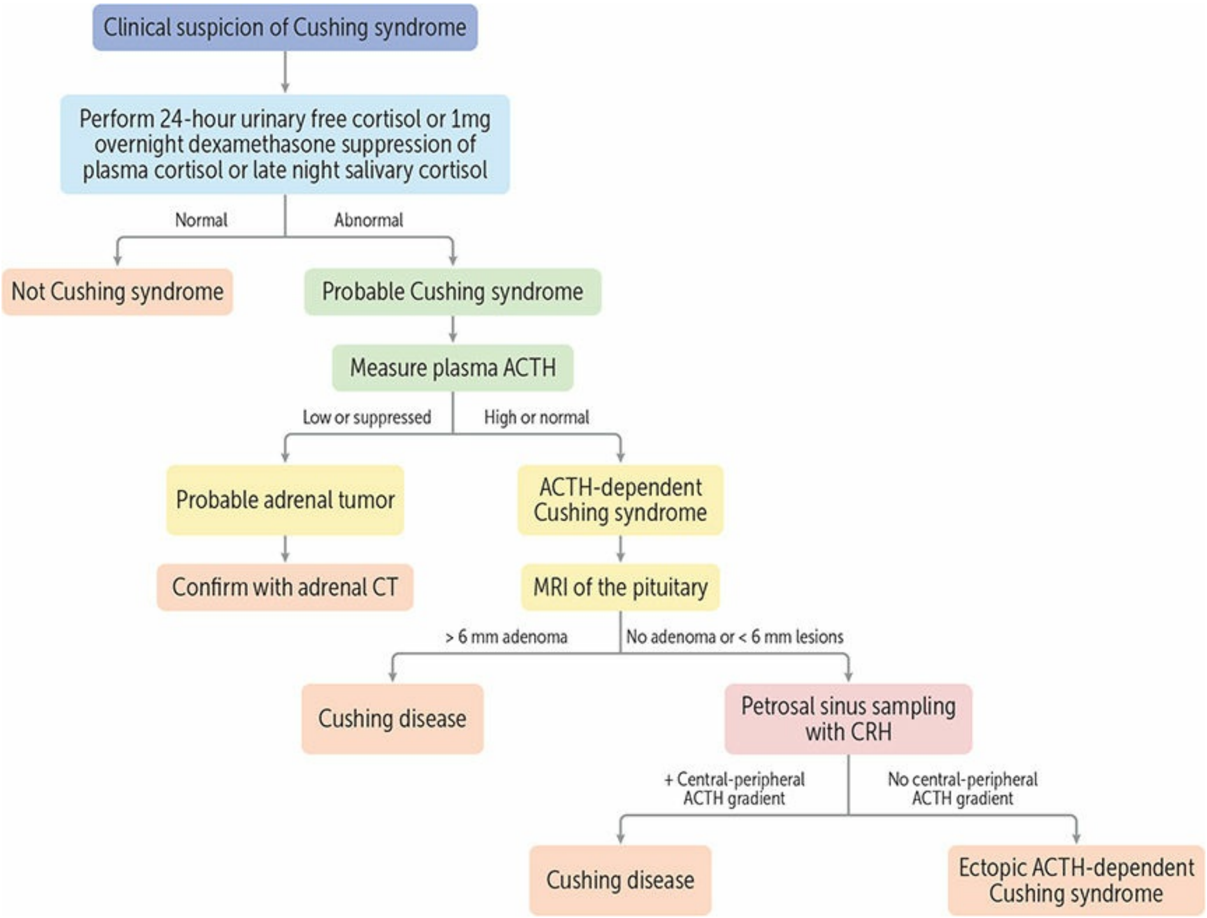

Clinical suspicion of Cushing syndrome
Perform 24-hour urinary free cortisol or 1mg overnight dexamethasone suppression of plasma cortisol or late night salivary cortisol
Normal
Abnormal
Not Cushing syndrome
Probable Cushing syndrome
Measure plasma ACTH
Low or suppressed
High or normal
Probable adrenal tumor
ACTH-dependent Cushing syndrome
Confirm with adrenal CT
MRI of the pituitary
> 6 mm adenoma
No adenoma or < 6 mm lesions
Cushing disease
Petrosal sinus sampling with CRH
+ Central-peripheral ACTH gradient
No central-peripheral ACTH gradient
Cushing disease
Ectopic ACTH-dependent Cushing syndrome

FIGURE 2.3-23. Diagnostic algorithm for Cushing syndrome. *ACTH*, Adrenocorticotropic hormone; CRH, corticotropin-releasing hormone. (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.3-13. Laboratory Findings in Cushing Syndrome

	CUSHING DISEASE (PITUITARY HYPERSECRETION)	EXOGENOUS STEROID USE	ECTOPIC ACTH SECRETION	ADRENAL CORTISOL HYPERSECRETION
24-hour urinary free cortisol	↑	↑	↑	↑
Salivary cortisol	↑	↑	↑	↑
ACTH	↑	↓	↑	↓
Dexamethasone suppression test morning cortisol level:		N/A[a]		N/A[a]
Low dose	↑		↑	
High dose	↓		↑	

[a] A dexamethasone suppression test is not required once the diagnosis of ACTH-independent Cushing syndrome is made.

KEY FACT

In Cushing disease, cortisol secretion remains elevated with the low-dose (1 mg) dexamethasone test but is suppressed with the high-dose (8 mg) dexamethasone test.

Treatment

- **Exogenous:** Gradual withdrawal and stoppage of glucocorticoids.
- **Endogenous:** Surgical resection of the source (pituitary, adrenal, ectopic neoplasm). Permanent hormone replacement therapy to correct deficiencies after treatment or resection of the primary lesion.

HYPERALDOSTERONISM

Hyperaldosteronism results from excessive secretion of aldosterone from the zona glomerulosa of the adrenal cortex. It is usually caused by bilateral adrenocortical hyperplasia (60%–70%) but can also result from unilateral adrenal adenoma (Conn syndrome).

History/PE

- Presents with hypertension, headache, polyuria, muscle weakness (caused by hypokalemia), and constipation/paralytic ileus (particularly if hypokalemia).
- Consider hyperaldosteronism in younger adults who are diagnosed with hypertension without risk factors or a family history of hypertension.

Diagnosis

- **Lab tests:** Can confirm 1° hyperaldosteronism with ↑ urinary aldosterone after oral sodium loading or saline infusion test (ie, failure to suppress aldosterone secretion). Hypokalemia, metabolic alkalosis, hypomagnesemia, hyperaldosteronism, ↑↑ aldosterone-to-plasma renin activity ratio (usually >30).
- **Imaging:** Only after labs. CT or MRI may reveal an adrenal mass.
- Adrenal venous sampling (will show ↑ aldosterone) may be needed to localize the adenoma or to confirm bilateral adrenal hyperplasia.

Treatment

- **Unilateral adenoma:** Surgical resection (after correction of BP and potassium).
- **Bilateral hyperplasia:** Aldosterone receptor antagonist (eg, spironolactone). Switch to eplerenone if side effects.

Q

An asymptomatic 36-year-old woman presents with a 2 cm thyroid mass. TFTs are unremarkable, but FNA reveals medullary carcinoma. Total thyroidectomy with thyroid hormone replacement is recommended. What are the most important screening tests to perform prior to surgery?

CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia (CAH) refers to genetic enzyme defects that impair cortisol synthesis, resulting in glucocorticoid insufficiency and buildup of precursors. Most cases are caused by 21-hydroxylase deficiency (95%, autosomal recessive), but other causes include 11- and 17-hydroxylase deficiencies.

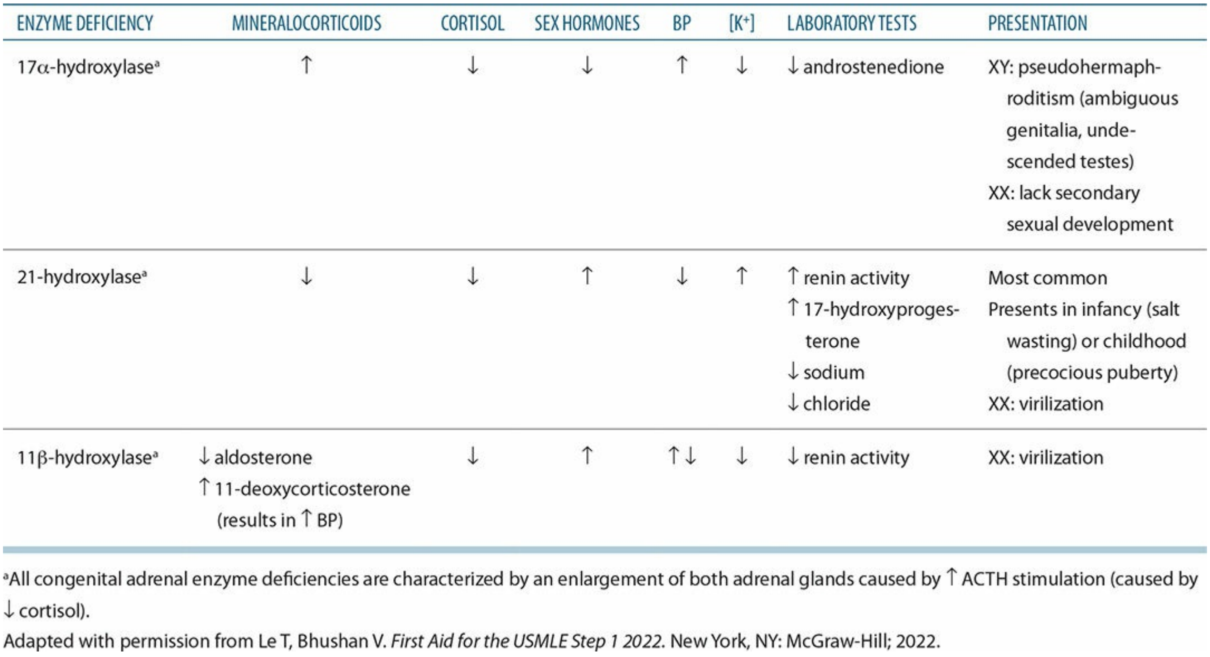
MNEMONIC

For CAH, if the deficient enzyme begins with 1 (**1**1 and **1**7), mineralocorticoid activity is high. If it ends with 1 (1**1** and 2**1**), androgen activity is high.

History/PE

See Table 2.3-14.

TABLE 2.3-14. Overview of Congenital Adrenal Hyperplasia



ENZYME DEFICIENCY	MINERALOCORTICOIDS	CORTISOL	SEX HORMONES	BP	$[K^+]$	LABORATORY TESTS	PRESENTATION
17α-hydroxylase[a]	↑	↓	↓	↑	↓	↓ androstenedione	XY: pseudohermaphroditism (ambiguous genitalia, undescended testes) XX: lack secondary sexual development
21-hydroxylase[a]	↓	↓	↑	↓	↑	↑ renin activity ↑ 17-hydroxyprogesterone ↓ sodium ↓ chloride	Most common Presents in infancy (salt wasting) or childhood (precocious puberty) XX: virilization
11β-hydroxylase[a]	↓ aldosterone ↑ 11-deoxycorticosterone (results in ↑ BP)	↓	↑	↑↓	↓	↓ renin activity	XX: virilization

[a] All congenital adrenal enzyme deficiencies are characterized by an enlargement of both adrenal glands caused by ↑ ACTH stimulation (caused by ↓ cortisol).

Adapted with permission from Le T, Bhushan V. *First Aid for the USMLE Step 1 2022*. New York, NY: McGraw-Hill; 2022.

Diagnosis

- **Lab tests:** Electrolyte abnormalities (see Table 2.3-14). In severe cases, mineralocorticoid deficiency may lead to life-threatening salt wasting.
- Elevated serum 17-hydroxyprogesterone level is diagnostic of 21-hydroxylase deficiency.

Treatment

- Immediate fluid resuscitation and salt repletion. Administer cortisol to ↓ ACTH and adrenal androgens. Fludrocortisone is appropriate for severe 21-hydroxylase deficiency.
- Possible surgical correction of ambiguous genitalia.
- Refer to the Gynecology chapter for information on the diagnosis and treatment of late-onset CAH.

KEY FACT

Congenital aromatase deficiency will present similarly to CAH in female newborns with external virilization and ambiguous external genitalia. However, the patient will have no electrolyte or blood pressure abnormalities.

The most important screening tests to perform are vanillylmandelic acid (VMA) and metanephrines. Medullary carcinoma of the thyroid is associated with MEN type 2A/2B, an autosomal dominant condition that predisposes patients not only to medullary carcinoma but also to pheochromocytomas. Screening for pheochromocytoma with urine VMA and metanephrines prior to surgery can prevent potentially life-threatening hypertensive crises during thyroidectomy.

MULTIPLE ENDOCRINE NEOPLASIAS

A family of tumor syndromes with autosomal dominant inheritance (see Fig. 2.3-24).

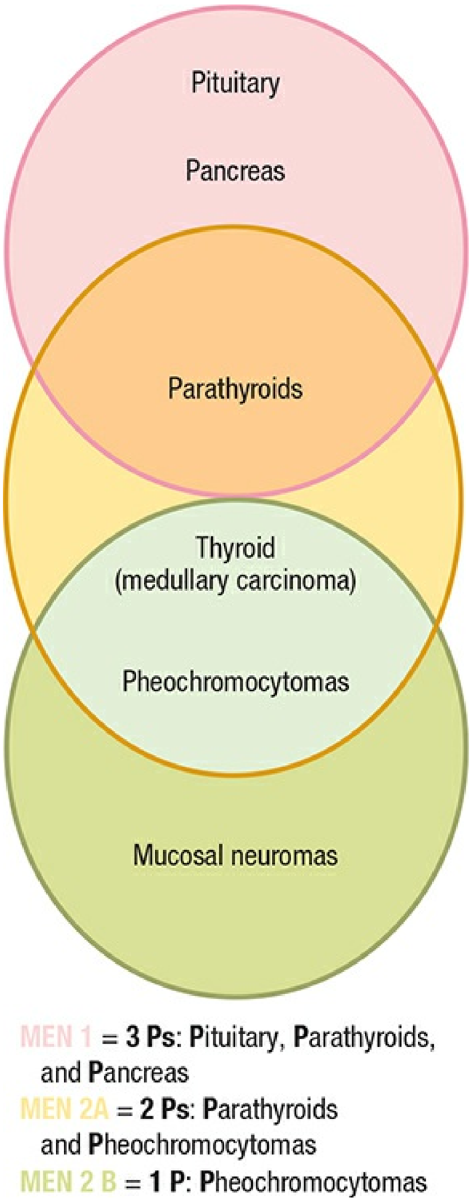

Pituitary
Pancreas
Parathyroids
Thyroid (medullary carcinoma)
Pheochromocytomas
Mucosal neuromas
MEN 1 = 3 Ps: Pituitary, Parathyroids, and Pancreas
MEN 2A = 2 Ps: Parathyroids and Pheochromocytomas
MEN 2 B = 1 P: Pheochromocytomas

FIGURE 2.3-24. **Multiple endocrine neoplasias (MEN).** (Modified with permission from UMSLE-Rx.com.)

MEN type 1 (formerly Wermer syndrome):

- Pancreatic islet cell tumors
  - Gastrinomas: Zollinger-Ellison syndrome

    - Insulinomas: Recurrent hypoglycemia with elevated insulin and C-peptide levels
    - VIPomas: Watery diarrhea, hypokalemia, and hypochlorhydria
    - Glucagonomas: New-onset diabetes, necrolytic migratory erythema
- Parathyroid adenomas
- Pituitary adenomas

MEN type 2A (formerly Sipple syndrome): Medullary carcinoma of the thyroid, pheochromocytoma, parathyroid hyperplasia/adenoma(s), parathyroid hyperplasia/adenoma(s). Caused by mutations in the *RET* proto-oncogene.

MEN type 2B: Medullary carcinoma of the thyroid, pheochromocytoma, oral and intestinal ganglioneuromatosis (mucosal neuromas), marfanoid habitus. Caused by mutations in the *RET* proto-oncogene.

NOTES

HIGH-YIELD FACTS IN

EPIDEMIOLOGY

Assessment of Disease Frequency

Person-Time Estimate

Assessment of Diagnostic Studies
- SENSITIVITY AND SPECIFICITY
- POSITIVE AND NEGATIVE PREDICTIVE VALUES
- LIKELIHOOD RATIO

Measures of Effect

Types of Clinical Studies
- CROSS-SECTIONAL STUDY
- COHORT STUDY
- CASE-CONTROL STUDY
- RANDOMIZED CONTROLLED TRIAL
- PHASES OF CLINICAL TRIALS

Evaluating Clinical Studies
- BIAS
- STATISTICAL TESTING
- SCENARIOS
- COMMONLY USED STATISTICAL TESTS

Prevention

Vaccination
- COVID-19 VACCINES

Screening Recommendations

Reportable Diseases

ASSESSMENT OF DISEASE FREQUENCY

The prevalence of a disease is the number of existing cases in the population at a specific moment in time.

$$\text{Prevalence} = \frac{\text{total number of cases in the population at one point in time}}{\text{total population}}$$

The incidence of a disease is the number of new cases in the disease-free population (“population at risk”) that develop over a period of time.

$$\text{Incidence} = \frac{\text{number of new cases in the population over a given time period}}{\text{total population at risk during the specified time period}}$$

KEY FACT

As the mortality of a disease ↓, the prevalence of that disease ↑ (eg, type 2 diabetes mellitus), because the duration of disease has lengthened. Remember: P = I × D.

KEY FACT

Incidence can be measured in a cohort study; prevalence can be measured in a cross-sectional study.

Prevalence is directly related to incidence and duration of disease. It is given by the following formula:

$$\text{Prevalence (P)} = \text{incidence (I)} \times \text{average duration of disease (D)}$$

For example, a chronic disease such as type 2 diabetes mellitus (DM) is diagnosed frequently, but due to improvements in treatment, people live longer with this disease. Thus the prevalence of type 2 DM increases daily as more people are diagnosed and more people with the disease live for a longer period.

For incidence, remember to subtract any preexisting cases of the disease from the total population at risk, as these individuals are no longer at risk.

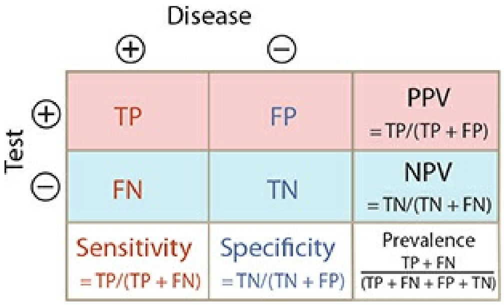
PERSON-TIME ESTIMATE

To further estimate the actual time at risk that all patients contributed to a study, a person-time estimate is calculated. This is relevant in cohort studies, as this considers when a person enters the study, leaves the study, or develops disease by taking into consideration four major end points: presence of disease at the onset of the study, death of the subject being studied, loss to follow-up, and end of the study.

ASSESSMENT OF DIAGNOSTIC STUDIES

SENSITIVITY AND SPECIFICITY

Physicians often use tests to narrow and confirm possible diagnoses. The sensitivity and specificity of these tests allow physicians to determine how often false ⊕ and false ⊖ results occur (Fig. 2.4-1). Both sensitivity and specificity are independent of disease prevalence.



	Disease		
	⊕	⊖	
Test ⊕	TP	FP	PPV = TP/(TP + FP)
⊖	FN	TN	NPV = TN/(TN + FN)
	Sensitivity = TP/(TP + FN)	Specificity = TN/(TN + FP)	Prevalence $\frac{TP + FN}{(TP + FN + FP + TN)}$

FIGURE 2.4-1. **Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).** Presence or absence of disease is typically assessed using a "gold standard" test, or the most accurate test available for a given disease. *TP*, true positive; *FP*, false positive; *FN*, false negative; *TN*, true negative. (Reproduced with permission USMLE-Rx.com.)

- **Sensitivity:** The probability that a patient with a disease will have a ⊕ test result.
  - A sensitive test rarely misses identifying people with the disease and is therefore good at ruling out those who do not have the disease. A high sensitivity means there is a low false ⊖ rate.
  - High sensitivity is desirable early in a diagnostic workup or screening test, when it is necessary to reduce a broad differential diagnosis.
  - Example: An initial enzyme-linked immunosorbent assay (ELISA) test for HIV infection.

False ⊖ rate = 1 – sensitivity = 1 – (TP/[TP + FN])

MNEMONIC

SNOUT—SeNsitive tests rule **OUT** disease.
SPIN—SPecific tests rule **IN** disease.

- **Specificity:** The probability that a patient without a disease will have a ⊖ test result.
  - A specific test rarely determines that someone has the disease when they do not and is therefore good at ruling in those who have the disease. A high specificity means there is a low false ⊕ rate.
  - High specificity is desirable when confirming a likely diagnosis.↑ specificity ↓ the number of false ⊕ results.
  - Example: A Western blot confirmatory HIV test.

False ⊕ rate = 1 – specificity = 1 – (TN/[TN + FP])

- The ideal test is both sensitive and specific, but a trade-off must often be made between sensitivity and specificity (Fig. 2.4-2). For a given test, when sensitivity ↑, specificity ↓ (and vice versa).

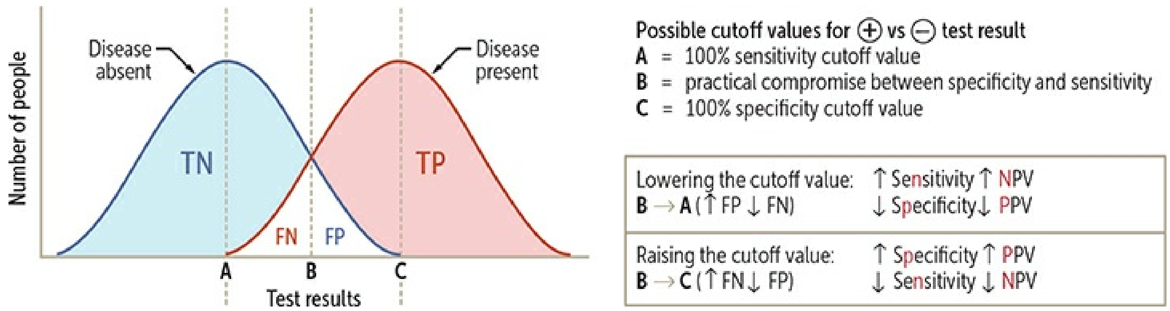


FIGURE 2.4-2. **Effect of cutoff values on sensitivity and specificity.** *FN*, False negative; *FP*, false positive; *TN*, true negative; *TP*, true positive. (Reproduced with permission from USMLE-Rx.com.)

- Occasionally, the USMLE asks students to compare different diagnostic tests using receiver operating characteristic (ROC) curves, where sensitivity is plotted on the *y*-axis and 1 – specificity is plotted on the *x*-axis (Fig. 2.4-3). The best diagnostic test will have a curve that “hugs” the *x*- and *y*-axes (curve X).

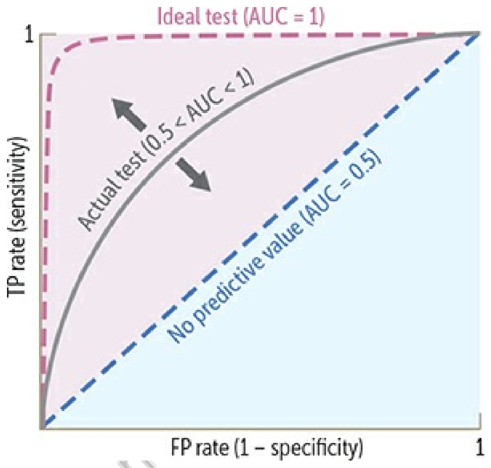


FIGURE 2.4-3. **Receiver operating characteristic curves.** The better performing test will have a higher AUC, with the curve closer to the upper left corner. (Reproduced with permission of USMLE-Rx.com.)

Q 1

What happens to the PPV and NPV when prevalence ↓?

Q 2

A local child care center that was built before the 1950s was found to have elevated lead levels in its paint. A student organization at your medical school is hosting a lead-screening event to test all children at the center. Which initial screening test would be more appropriate: a test that has high sensitivity or one that has high specificity?

Q 3

Your hospital is considering adopting a new diagnostic test for pheochromocytoma. In Figure 2.4-2, the current diagnostic test (urinary metanephrines) falls close to point B. The new test falls closer to point A. How will the false ⊕ and false ⊖ rates of this new test compare to urinary metanephrines?

POSITIVE AND NEGATIVE PREDICTIVE VALUES

Once a test has been administered and a patient’s result has been made available, that result must be interpreted through use of predictive values. Remember, unlike sensitivity and specificity, which refer to test characteristics, PPV and NPV depend both on the test characteristics and the underlying disease prevalence.

- **PPV:** The probability that a patient with a ⊕ test result truly has the disease. The higher the disease prevalence, the higher the PPV of the test for that disease. A change in the test cutoff point that ↑ false ⊕ will ↓ the PPV. This means that with an increase in the specificity of the test, there is an increase in the PPV, and vice versa.
- **NPV:** The probability that a patient with a ⊖ test result truly does not have the disease. The lower the disease prevalence, the higher the NPV of the test for that disease. A change in the test cutoff point that ↑ false ⊖ will ↓ the NPV. This means that with an increase in the sensitivity of a test, there is an increase in the NPV, and vice versa.

LIKELIHOOD RATIO

The likelihood ratio (LR) expresses the extent to which a given test result is likely in diseased people as opposed to people without disease:

- LR ⊕ shows how much the odds (or probability) of disease are ↑ if the test result is ⊕.
- LR ⊖ shows how much the odds (or probability) of disease are ↓ if the test result is ⊖.

$$\text{LR}\oplus = \text{sensitivity}/(1 - \text{specificity})$$

$$\text{LR}\ominus = (1 - \text{sensitivity})/\text{specificity}$$

$$\text{Posttest odds} = \text{pretest odds} \times \text{LR}$$

1 **A**

PPV ↓ and NPV ↑. Remember that if prevalence is low, even a test with high sensitivity or specificity will have a low PPV.

2 **A**

A test with high sensitivity, such as a fingerstick lead test (capillary blood), is preferred for initial screening because it can ensure that no children who might have the disease—and who might benefit from further testing and treatment—will be missed. The children with a ⊕ fingerstick test should subsequently have a serum blood level drawn (higher specificity).

3 **A**

The false ⊕ rate will ↑ (capturing more of the “no disease” cohort), but the false ⊖ rate will ↓ (capturing the little tail of the “disease” cohort). In Fig. 2.4-2, this translates to ↑ sensitivity and ↓ specificity.

MEASURES OF EFFECT

A central aim of epidemiology is to assess the relationship between an exposure event and an outcome measure. The likelihood or risk of observing an outcome following an exposure is quantified using measures of effect. Ways to express and compare risk include the following:

- **Absolute risk:** The incidence of disease.
- **Relative risk (or risk ratio; RR):** Expresses how much more likely an exposed person is to get the disease in comparison to an unexposed person. This indicates the relative strength of the association between exposure and disease, making it useful when one is considering disease etiology. This is used mostly in **cohort** studies.

$$\text{RR} = \frac{\text{incidence in exposed}}{\text{incidence in unexposed}}$$

RR > 1 suggests ↑ risk

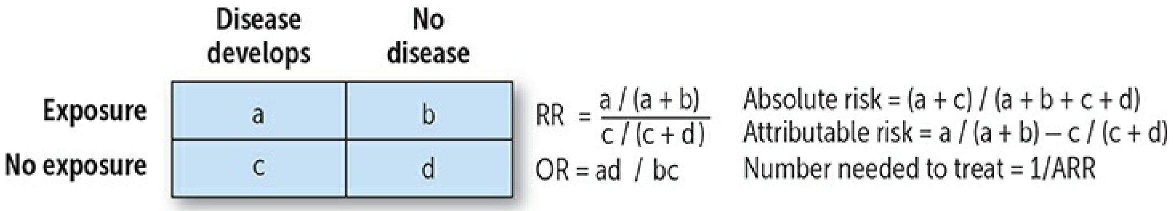
RR < 1 suggests ↓ risk

- **Attributable risk (or risk difference):** The difference in risk between exposed and unexposed groups.

Attributable risk = (incidence of disease in exposed − incidence in unexposed)

Attributable risk percentage = [(RR − 1)/RR] × 100%

- **Absolute risk reduction (ARR):** The difference in risk that is attributable to the intervention compared to a control. From the 2 × 2 table (see example in Fig. 2.4-4), ARR is derived as:



	Disease develops	No disease
Exposure	a	b
No exposure	c	d

$\text{RR} = \dfrac{a/(a+b)}{c/(c+d)}$

OR = ad / bc

Absolute risk = (a + c) / (a + b + c + d)

Attributable risk = a / (a + b) – c / (c + d)

Number needed to treat = 1/ARR

FIGURE 2.4-4. **Relative risk (RR) vs odds ratio (OR).** (Adapted with permission from USMLE-Rx.com.)

ARR = (c/[c + d]) – (a/[a + b])

- **Number needed to treat (NNT):** Number of individuals who need to be treated for one patient to benefit.

NNT = 1/absolute risk reduction

- **Odds ratio (OR):** An estimate of relative risk that is used in case-control studies, ie, it represents the odds of exposure among cases vs odds of exposure among controls. The OR tells how much more likely it is that a person with a disease has been exposed to a risk factor than someone without the disease. The lower the disease prevalence, the more closely it approximates RR. In case-control studies, the OR also describes how many times more likely an exposed individual is to have disease compared to an unexposed individual (see Fig. 2.4-4).

$$\text{OR} = \frac{\text{odds that a diseased person is exposed}}{\text{odds that a nondiseased person is exposed}}$$

Once a diagnosis has been established, it is important to be able to describe the associated prognosis. Survival analysis is used to summarize the average time from one event (eg, presentation, diagnosis, or start of treatment) to any outcome that can occur only once during follow-up (eg, death or recurrence of cancer). The usual method is with a Kaplan-Meier curve (Fig. 2.4-5) describing the survival in a cohort of patients, with the probability of survival ↓ over time as patients die or drop out from the study.

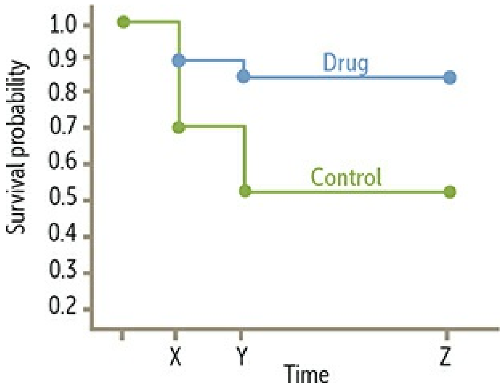


FIGURE 2.4-5. Example of a Kaplan-Meier curve. (Reproduced with permission from USMLE-Rx.com.)

- **Hazard ratio (HR):** An estimate of the chances that an event occurs in the treatment arm of a trial vs the nontreatment arm. Used in prospective studies. Values <1 indicate that the treatment arm had a ↓ in the event rate, and values >1 indicate the event rate ↑. A value of 1 suggests lack of association.

HR = hazard in treatment arm/hazard in control arm

Q

Assume that the data below are from a hypothetical case-control study. Calculate and interpret the OR.

		EXPOSED	
		YES	NO
Disease Status	Cases	283	263
	Controls	182	210

TYPES OF CLINICAL STUDIES

Studies are typically used to evaluate diagnosis, treatment, and screening for a disease. Although the gold standard for such evaluation is a randomized, double-blind controlled trial, other types of studies may be used as well (eg, an observational study, in which the exposure in question is a therapeutic intervention). Figure 2.4-6 illustrates the level of evidence pyramid. At the bottom of the pyramid are low level of evidence studies, and at the top of the pyramid are high level of evidence studies. In descending order of strength of evidence, published studies regarding treatment options include randomized controlled trials (RCTs); observational studies like case-control, cohort, and cross-sectional studies; and case series/case reports. Meta-analyses are often used to systematically synthesize information across studies to help summarize the totality of the evidence. Randomization is successful when the baseline characteristics of patients in each group are statistically similar.

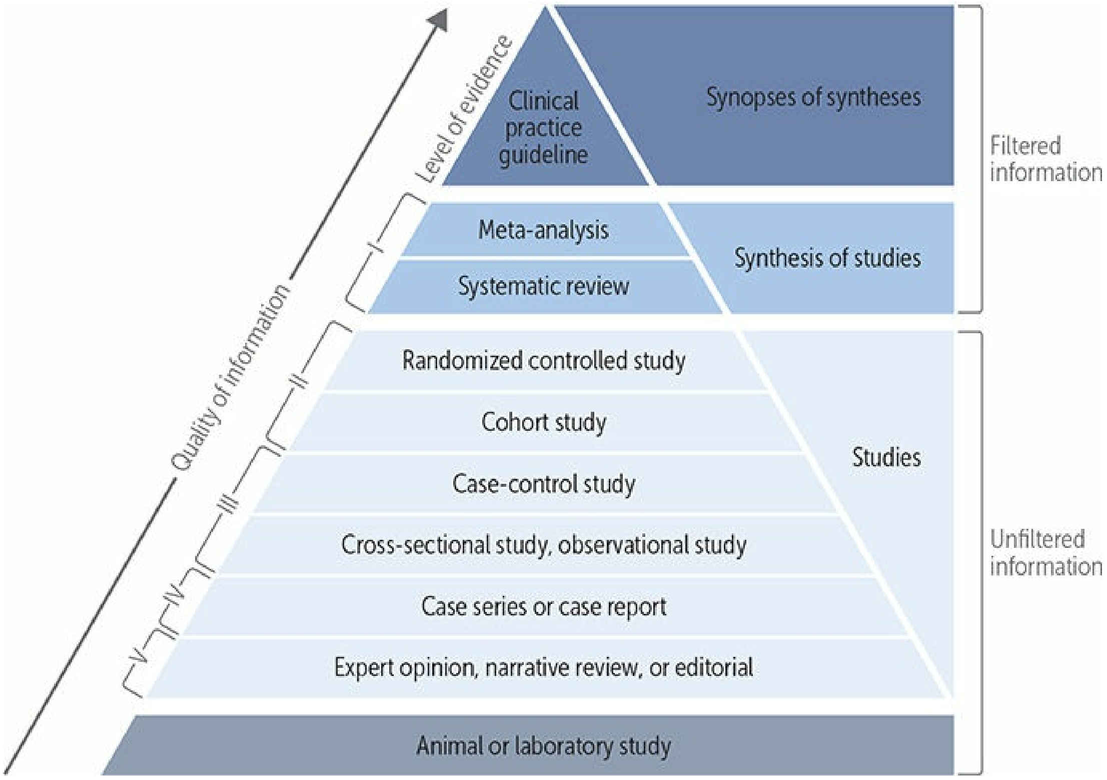

Level of evidence
Quality of information
Clinical practice guideline
Synopses of syntheses
Filtered information
Meta-analysis
Systematic review
Synthesis of studies
I
Randomized controlled study
II
Cohort study
III
Case-control study
Cross-sectional study, observational study
IV
Case series or case report
V
Expert opinion, narrative review, or editorial
Studies
Unfiltered information
Animal or laboratory study

FIGURE 2.4-6. **Strength of evidence in increasing order.** (Reproduced with permission from USMLE-Rx.com.)

CROSS-SECTIONAL STUDY

A cross-sectional study is an observational study that assesses risk factors and outcomes at a snapshot in time (Fig. 2.4-7). This study does not prove temporal relationships because it measures correlation, not causation. The most common example of this type of study would be a general survey or a census.

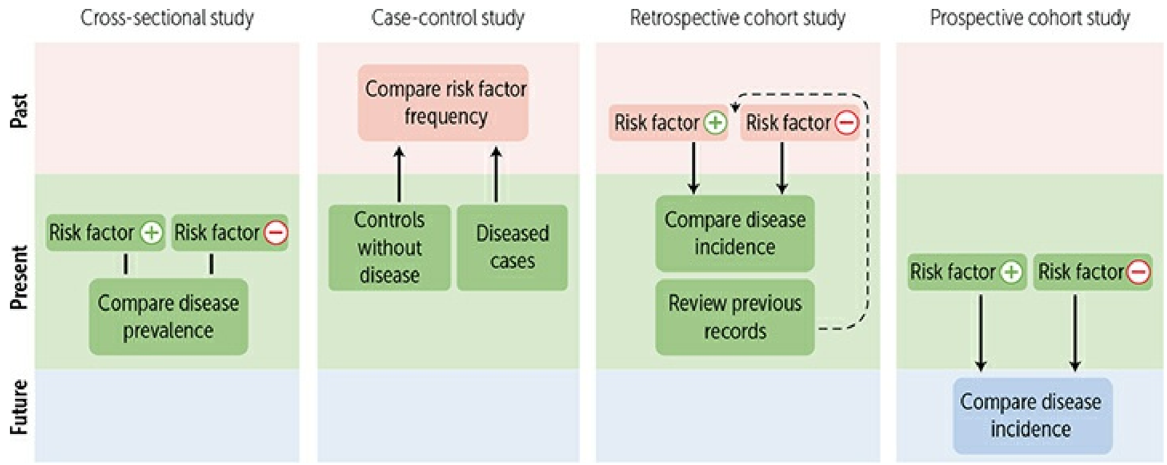

Cross-sectional study
Case-control study
Retrospective cohort study
Prospective cohort study
Past
Present
Future
Risk factor ⊕
Risk factor ⊖
Compare disease prevalence
Compare risk factor frequency
Controls without disease
Diseased cases
Risk factor ⊕
Risk factor ⊖
Compare disease incidence
Review previous records
Risk factor ⊕
Risk factor ⊖
Compare disease incidence

FIGURE 2.4-7. **An overview of various observational studies.** (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

A cross-sectional study that is undertaken to estimate prevalence is called a prevalence study.

Advantages of cross-sectional studies include the following:

- They provide an efficient means of examining a population, allowing simultaneous assessment of people with the disorder and those without it.
- They can give a basis for diagnostic testing.

Disadvantages include the following:

- Cross-sectional studies only obtain information at a single point in time, so researchers cannot determine causal relationships.
- Risk or incidence of disease cannot be directly measured.

A

OR = ad/bc = (283 × 210)/(263 × 182) = 1.24

Interpretation: The exposed group had 1.24 times the odds of having disease compared to the unexposed group.

COHORT STUDY

In a cohort study, a group of people sharing certain characteristics (eg, age, gender, occupation, or date of birth) is assembled to study the relationships between exposures and outcomes of interest (see Fig. 2.4-7). For each possible risk factor, the members of the cohort are classified as either exposed or unexposed. All the cohort members are then followed over time, and the incidence of outcome events is compared in the two exposure groups.

Example: The Framingham Heart Study followed a group of men and women over time to see how different exposures (eg, diet, exercise, aspirin) affected the incidence of heart disease.

Advantages of cohort studies include:

- They provide the only way to directly determine incidence (because they follow a cohort over time to assess disease development).
- They let researchers assess the relationship of a given exposure to many diseases.
- In prospective studies, exposure is elicited without bias from a known outcome.

KEY FACT

Cohort studies are also known as longitudinal or prospective or incidence studies, from which both OR and RR can be calculated.

Disadvantages include the following:

- Cohort studies can be time-consuming and expensive.
- Studies only assess the relationship of the disease to the few exposures identified and measured as a part of the study.
- The requirement for many subjects makes it difficult to study rare diseases.

Cohort studies can be either prospective, in which a cohort is assembled in the present and followed into the future, or retrospective, in which a cohort is identified from past records and is followed to the present.

KEY FACT

In cohort studies, the researcher ascertains who is exposed or unexposed and follows them over time for disease development.

CASE-CONTROL STUDY

In a case-control study, a series of cases are identified and a set of controls is sampled from the underlying population to estimate the frequency of exposure in the population at risk for the outcome (see Fig. 2.4-7). In such a study, a researcher compares the frequency of exposure to a possible risk factor between the case and control groups.

Example: A study examines patients with heart disease (cases) and those without heart disease (controls) and compares exposures to red meat in both groups.

- Validity depends on appropriate selection of cases and controls, the way exposure is measured, and the ways in which a researcher deals with confounding variables.

KEY FACT

Accuracy and validity measure bias. Accuracy requires correct measurements. Precision (and reliability) measures random error. Precision ↑ with ↑ sample size.

- External validity (also known as generalizability) is the applicability of the results to a new population.
- Cases and controls should be comparable in terms of opportunity for exposure (ie, they should be members of the same base population with an equal opportunity of risk factor exposure).

- “Matching” occurs when the researcher chooses controls that match cases on a particular characteristic.
    - Example: If matching on sex, female cases would be matched to female controls and male cases would be matched to male controls.
    - The purpose of matching is to ↓ confounding.

KEY FACT

In case-control studies, the researcher controls the number of cases and controls. Only ORs can be calculated from case-control studies.

Advantages of case-control studies are as follows:

- They use smaller groups than cohorts, thereby reducing costs.
- They can be used to study rare diseases and can easily examine multiple risk factors. This is because in case-control studies, the OR is a close approximation of RR, known as “rare disease assumption.”

Disadvantages include the following:

- Case-control studies cannot calculate disease prevalence or incidence, and they cannot directly estimate the RR because the investigator—not nature—artificially determines the numbers of subjects with and without a disease. However, an OR determined via a case-control study can be used to estimate a measure of RR if the prevalence is low.
- Retrospective data can be inaccurate because of recall or survivorship biases.

RANDOMIZED CONTROLLED TRIAL

An RCT is an experimental, prospective study in which subjects are randomly assigned to a treatment or control group. Random assignment helps remove confounding and ensure that the two groups are truly comparable. The control group may be treated with a placebo or with the accepted standard of care.

The study can be masked in one of two ways: 1) single blind, in which patients do not know which treatment group they are in, or 2) double blind, in which neither the patients nor their physicians know who is in which group.

KEY FACT

Randomization minimizes bias and confounding; double-blind studies prevent observation bias.

- Double-blind studies are the gold standard for studying treatment effects.
- Factorial design involves several rounds of randomization with two or more variables.
    - Example: A trial studies the role of aspirin and statins in preventing myocardial infarction (MI) by creating four groups: one given aspirin only, one given statin only, one given both aspirin and statin, and one given neither. The rates of MI are then measured.

Advantages of RCTs are as follows (see also Table 2.4-1):

TABLE 2.4-1. Comparison of Study Designs

VARIABLE	RCT	COHORT	CROSS-SECTIONAL	CASE CONTROL
Purpose	Tests causality through random assignment of exposure	Follows groups of patients over a specified period to capture the association of risk factors to the development of disease	Determines prevalence in a snapshot of time	Tests association (usually retrospectively, but outcome first, then looks for risk factors)
Measures	Varied, including response to treatment, adverse effects, survival during follow-up	RR, OR, incidence, prevalence	Prevalence (not incidence)	OR
Design	Subjects are randomly assigned to be in treatment or placebo arms	Subjects are not assigned to groups Determines if subjects are in exposed or unexposed groups and follows them until they develop the disease (or do not)	Determines disease prevalence at one point in time; cannot determine the directionality of association between exposure and outcome	Identifies cases (disease) and controls (no disease) groups first and then goes backward to determine if they are exposed or not (the opposite of RCT and cohort studies)
Advantages	Can determine causality; minimizes bias and confounding	Temporality can be determined; incidence can be determined	Less time-consuming and costly	Predetermined number of cases; less time-consuming and costly
Disadvantages	RCT is not possible when: ▪ Treatment has a known adverse outcome ▪ Disease is very rare ▪ Treatment is in widespread use or represents the best option (because it is unethical to withhold treatment)	Follows large groups over long periods Selection bias in retrospective cohort studies	Directionality of association cannot be determined Incidence cannot be determined	Recall bias, selection bias

- They minimize bias.
- They have the potential to demonstrate causal relationships because exposure is assigned randomly, which minimizes confounding.
- Exposure to the treatment is assigned randomly while other characteristics in the groups are all similar.

Disadvantages include the following:

- RCTs are costly and time intensive.
- Some interventions (eg, surgery) are not amenable to blinding.

KEY FACT

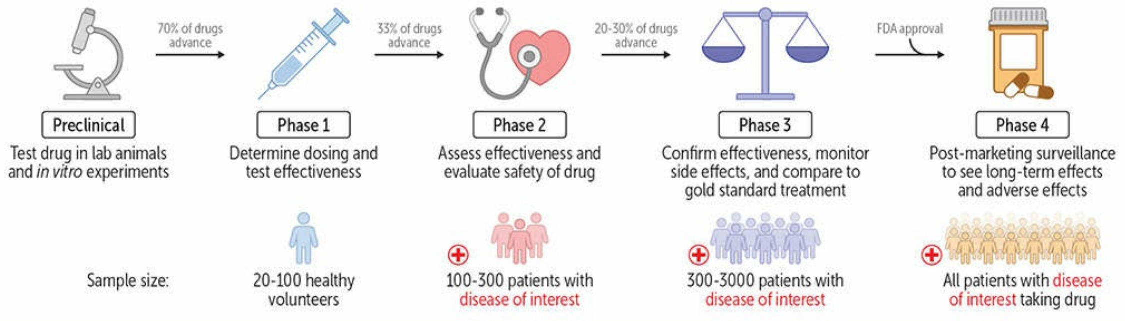
A drug is available in the market once it passes Phase 3.

PHASES OF CLINICAL TRIALS

A new drug must undergo several phases of testing before being placed on the market for public use. The phases include testing in animals, healthy volunteers, and small and large groups of patients with disease. Once the drug is on the market, mandatory reporting of adverse events is required during postmarketing surveillance. Table 2.4-2 lists details of these phases.

TABLE 2.4-2. **Phases of Clinical Treatment Trials**

PHASE	GOALS	NUMBER OF PARTICIPANTS	TYPE OF PARTICIPANTS
Preclinical	Understand mechanism of drug	N/A	Nonhuman
0	Study pharmacokinetics of drug in human body	Usually limited to 10	Healthy volunteers
1	Establish safety range of drug dosing	Anywhere from 20 to 100 participants	Healthy volunteers
2	Assess efficacy and adverse effects of drug	Anywhere from 100 to 300 participants	Patients with disease the drug is to treat
3	Assess safety and efficacy of drug	Anywhere from 300 to 3000 participants	Patients with disease the drug is to treat Compared to gold-standard treatment
4	Postmarketing surveillance to see long-term effectiveness and adverse effects	All patients taking the drug	Effects and adverse effects to be noted by treating physician


70% of drugs advance
33% of drugs advance
20-30% of drugs advance
FDA approval
Preclinical
Test drug in lab animals and in vitro experiments
Phase 1
Determine dosing and test effectiveness
Phase 2
Assess effectiveness and evaluate safety of drug
Phase 3
Confirm effectiveness, monitor side effects, and compare to gold standard treatment
Phase 4
Post-marketing surveillance to see long-term effects and adverse effects
Sample size:
20-100 healthy volunteers
100-300 patients with disease of interest
300-3000 patients with disease of interest
All patients with disease of interest taking drug

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EVALUATING CLINICAL STUDIES

BIAS

A bias in research is any process that causes results to systematically differ from the truth. Research can be biased before conduction, during conduction, and after completion (during analysis) (Fig. 2.4-8.)

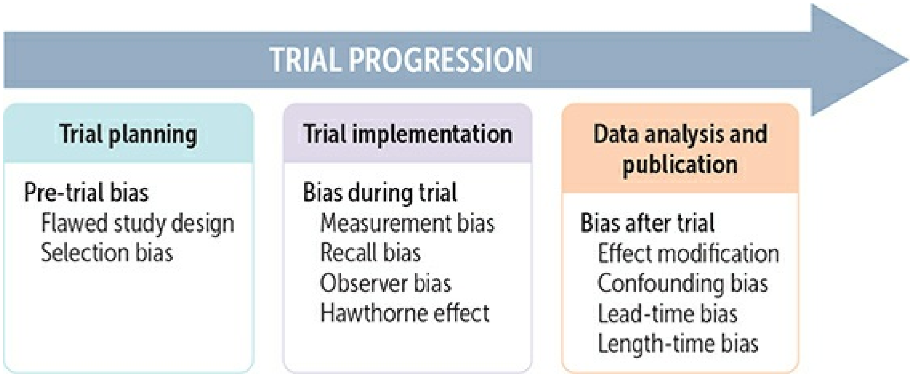

TRIAL PROGRESSION
Trial planning
Pre-trial bias
Flawed study design
Selection bias
Trial implementation
Bias during trial
Measurement bias
Recall bias
Observer bias
Hawthorne effect
Data analysis and publication
Bias after trial
Effect modification
Confounding bias
Lead-time bias
Length-time bias

FIGURE 2.4-8. **Major sources of bias in clinical trials.** (Reproduced with permission from USMLE-Rx.com.)

- **Selection bias:** Occurs when samples or participants are selected that differ from the study population in a meaningful way. Example: Individuals concerned about a family history of breast cancer may be more likely to self-select in entering a mammography program, giving the impression of a prevalence that is higher than it is in reality.
  - Example: If a substantial portion of subjects in one group are lost to follow-up (attrition bias), the study may overestimate the association. This is a special type of selection bias.
- **Measurement bias:** Occurs when measurement or data-gathering methods differ between groups.
  - Example: One group is assessed by CT, while another group is assessed by MRI.

KEY FACT

Studies that are masked and randomized are better protected from the effects of bias, whereas observational studies are particularly susceptiwble to bias.

- **Confounding bias:** Occurs when a third variable is either positively or negatively associated with both the exposure and outcome variables, inducing an incorrect association.
  - Example: Fishermen in an area may experience a higher incidence of lung cancer than that found in the general population. If people who smoke become fishermen, then by this logic they are also more likely to develop lung cancer than those who do not smoke (and yet become fishermen). So, in testing for an association between lung cancer and fishing, smoking would be a confounding variable.
- **Effect modification:** Occurs when a third variable disproportionately affects two groups. Effect modification shows a meaningful difference, whereas confounding does not. This can be identified by use of stratified analysis (ie, a subgroup analysis of the cohort).
  - Example: A study shows that a new chemotherapeutic agent only modestly improves survival rates in some patients with non-Hodgkin lymphoma. However, investigators noted that those patients >65 years of age had significant survival benefits, whereas those below the age of 65 years did not. In this case age is an effect modifier.

KEY FACT

Confounding variables reduce the internal validity of a study.

- **Recall bias:** Results from a difference in the retrospective recall of past factors or outcomes.
  - Example: A patient with cancer may be more motivated to recall past episodes of chemical exposure than would a healthy individual.
  - Example: A mother whose child has neural tube defects may likely recall more about lack of folate supplementation during early pregnancy than a mother with a healthy child.
- **Observer bias:** Results from investigator’s awareness of the population being studied and its exposure status.

    - Example: A trial for new blood pressure management in the intensive care unit (ICU) is biased when the attending physician knows which patients are enrolled in the treatment arm.
- **Hawthorne effect:** Results from study subjects’ awareness that they are being studied, causing them to change aspects of their behavior.
    - Example: Employees at an automotive factory may work more productively when they realize that their superiors are conducting random audits.
- **Lead-time bias:** Results from earlier detection of disease, giving an appearance of prolonged survival when in fact the natural course is not altered.
    - Example: A new and widely used screening test that detects cancer 5 years earlier may yield the impression that patients are living longer with the disease.
- **Length bias:** Occurs when screening tests detect a disproportionate number of slowly progressive diseases but miss rapidly progressive ones, leading to overestimation of the benefit of the screen.
    - Example: A better prognosis for patients with cancer is celebrated, following the implementation of a new screening program. However, this test disproportionately detects slow-growing tumors, which generally tend to be less aggressive.

Q

A hypothetical study finds a ⊕ association between poor sleep habits and the risk for Parkinson disease. The RR is 10, and the *P* value is 0.4. How do you interpret these results?

STATISTICAL TESTING

Even with bias reduction, unsystematic random error is unavoidable because of chance variation in studied data. Types of errors are as follows:

- **Type I (α) error:**
    - A type I/α error is the probability of concluding that there is a difference in treatment effects between groups when in fact there is not (eg, a false ⊕ conclusion)—in other words, rejecting the null hypothesis (of no effect) when it should not be rejected.
    - The ***P*** value is an estimate of the probability that differences in treatment effects in a study could have happened by chance alone if no true association exists. A ***P value of*** **<0.05** is considered statistically significant in medical literature but may not always imply clinical significance (usually noted with meta-analysis where the sample size is large enough to identify a small but clinically insignificant difference in outcome). A *P* value alone does not give any information about the direction or size of the effect.
- **Type II (β) error:**
    - A type II/β error is the probability of concluding that there is no difference in treatment effects when in fact a difference exists (eg, a false ⊖ conclusion)—in other words, not rejecting the null hypothesis (of no effect) when it should be rejected.
    - Power is the probability that a study will find a statistically significant difference when one is truly there. Increasing the number of subjects in a study increases the power. A lower type II error leads to an increase in the power of the study. Similarly, larger effect size would lead to an increase in power and a decrease in need of a large study sample.

$$\text{Power} = 1 - \text{type II error } (\beta)$$

The confidence interval (CI) is a way of expressing statistical significance that shows the size of the effect and the statistical power (the narrower the CI, the greater the statistical power). CIs are interpreted as follows:

- If one is using a 95% CI, there is a 95% chance that the interval contains the true value.
- Larger sample sizes produce more power and narrower CIs. If the CI includes the null value (RR of 1.0 or 0), the results are not statistically significant.
- Example: An RCT studying aspirin to prevent MI shows an RR of 0.9 with a 95% CI of 0.85 to 0.95 in a sample of 3000 patients, whereas in a sample of 30 patients the 95% CI is 0.1 to 1.7. The first example shows a significant difference, whereas the second does not.

A

There is no sufficient evidence to reject the null hypothesis, and therefore there is insufficient evidence to support an association between poor sleep habits and the risk for Parkinson disease. Remember that the null hypothesis always assumes that there is no association between the exposure and outcome variables. If the ***P*** value is >0.05, then you cannot reject the null hypothesis.

SCENARIOS

In a scenario where we are trying to study the effect of drug X on multiple sclerosis, the null hypothesis states that drug X is not effective for multiple sclerosis. If the statistical testing shows:

- *P >0.05*, the null hypothesis is not rejected (there is a risk of type II/β **error**) **ie, drug X is not effective.**
- *P ≤0.05*, the null hypothesis is rejected and statistical significance is reached (there is a risk of type I/α **error**) **ie, drug X is effective for multiple sclerosis.**

Important limitations of P value:

- It does not quantify the strength of benefit derived from or the effect size of an intervention or exposure on individual subjects.
- It is usually arbitrarily defined to be significant if it is less than or equal to 0.05. This means that there is still a 5% risk of type I/α error even in a statistically significant result.
- It does not tell whether an individual patient will derive the same benefit as the whole group.

COMMONLY USED STATISTICAL TESTS

Tests can be used to evaluate either categorical data or numerical data (see Fig. 2.4-9). These are used to represent data and assess if there is any statistically significant difference between two or more groups that are compared.

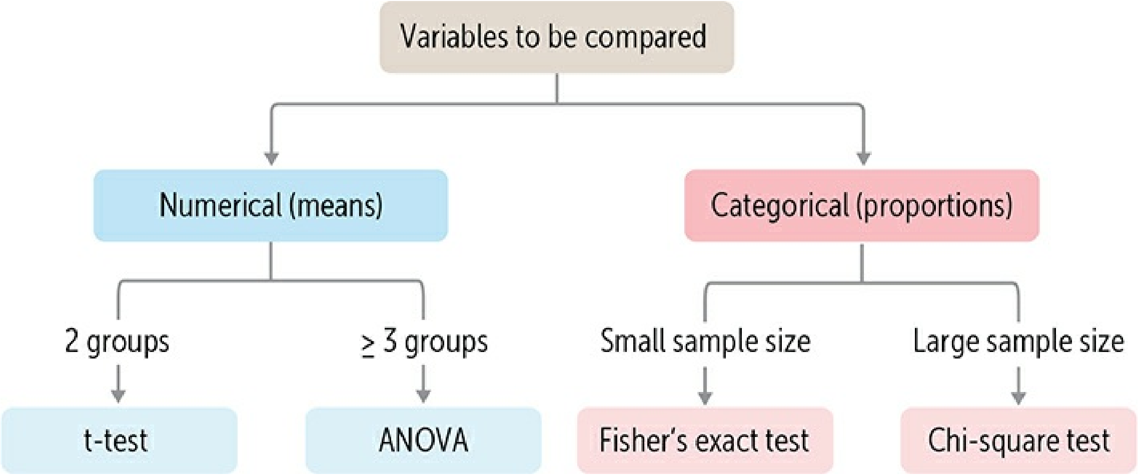


FIGURE 2.4-9. **Choosing statistical tests for numerical and categorical data.** (Reproduced with permission from USMLE-Rx.com.)

- **Descriptive statistics:** Includes common measures like mean, median, and mode as measures of central tendency and interquartile range, standard deviation, and variance as measures of variability.
- **t-test:** Used to check the difference between means of two variables.
- **Analysis of variance (ANOVA):** Used to check the difference among means of three or more variables.
- **Fisher's exact test:** Used to assess differences between two categorical variables when the sample size is small.
- **Chi-square (χ^2) test:** Used to assess differences between two or more categorical variables when the sample size is large. This test is only an approximation (vs Fischer's exact test) in a large population.
- **Correlation:** Used to assess if change in one variable is directly linked to change in another variable. Used mostly for continuous variables.
- **Logistic regression:** Used to describe data and explain the relationship between one dependent categorical (binary) variable and one or more independent variables.
- **Linear regression:** Used to predict the value of one dependent continuous variable based on the value of one or more independent variables.

PREVENTION

There are three levels of prevention:

- **Primary prevention:** Includes preventive measures to ↓ the incidence of disease in unaffected individuals.
- **Secondary prevention:** Focuses on identifying the disease early, when it is asymptomatic or mild, and implementing measures that can halt or slow disease progression. Includes screening tests that are designed to identify subclinical disease.
- **Tertiary prevention:** Includes measures that ↓ morbidity or mortality resulting from the presence of disease.
- **Quaternary prevention:** Includes measures to minimize harm from incidents during treatment.

Prevention may be accomplished by a combination of immunization, chemoprevention, behavioral counseling, and screening. A good screening test has the following characteristics:

- High sensitivity and specificity (usually more important to have high sensitivity to rule out those who do not have the disease)

- High NPV
- Inexpensive, easy to administer, and safe
- Treatment after screening is more effective than subsequent treatment without screening

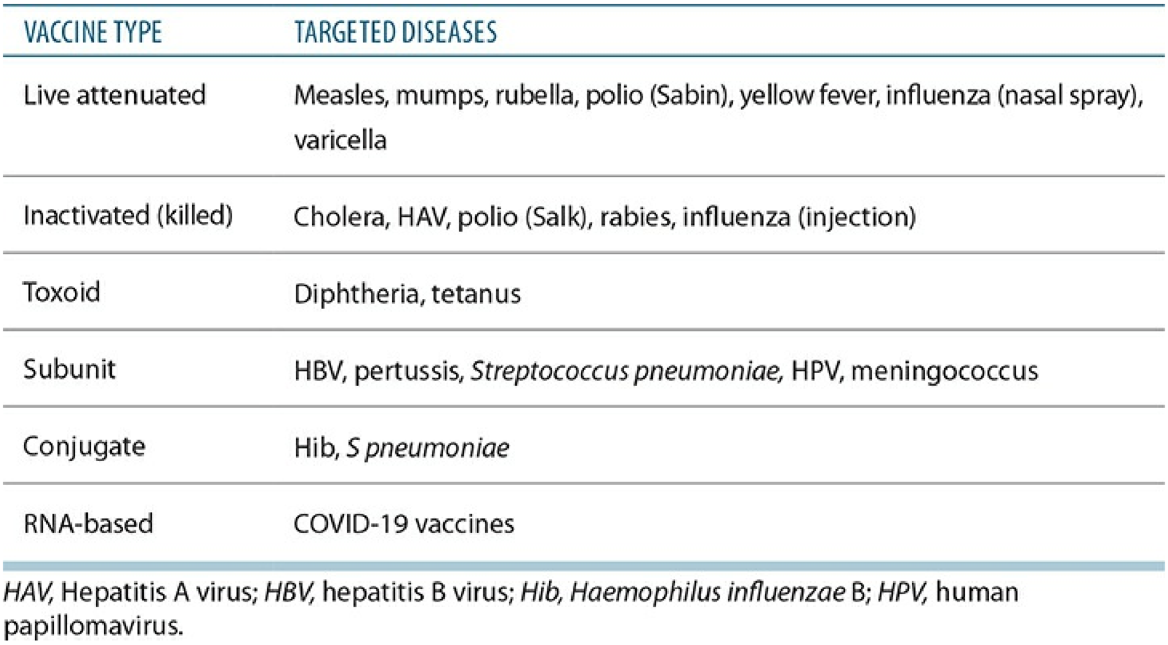
KEY FACT

Examples of levels of prevention:
Primary: ↓ dietary fat/alcohol intake to reduce risk for breast cancer.
Secondary: Routine mammograms to screen for breast cancer.
Tertiary: Adjuvant therapy with tamoxifen for breast cancer.
Quaternary: Identification of a potential polypharmacy-induced interaction prior to dispensing medications.

VACCINATION

Vaccines work by mimicking infections and triggering an immune response in which memory cells are formed to recognize and fight any future infection. They work as a mode of primary prevention. There are several different vaccine formulations, as indicated in Table 2.4-3.

TABLE 2.4-3. Types of Vaccinations



VACCINE TYPE	TARGETED DISEASES
Live attenuated	Measles, mumps, rubella, polio (Sabin), yellow fever, influenza (nasal spray), varicella
Inactivated (killed)	Cholera, HAV, polio (Salk), rabies, influenza (injection)
Toxoid	Diphtheria, tetanus
Subunit	HBV, pertussis, *Streptococcus pneumoniae*, HPV, meningococcus
Conjugate	Hib, *S pneumoniae*
RNA-based	COVID-19 vaccines

HAV, Hepatitis A virus; *HBV*, hepatitis B virus; *Hib*, *Haemophilus influenzae* B; *HPV*, human papillomavirus.

Recommended vaccination schedules for children and adults are outlined in Figures 2.4-10 and 2.4-11.

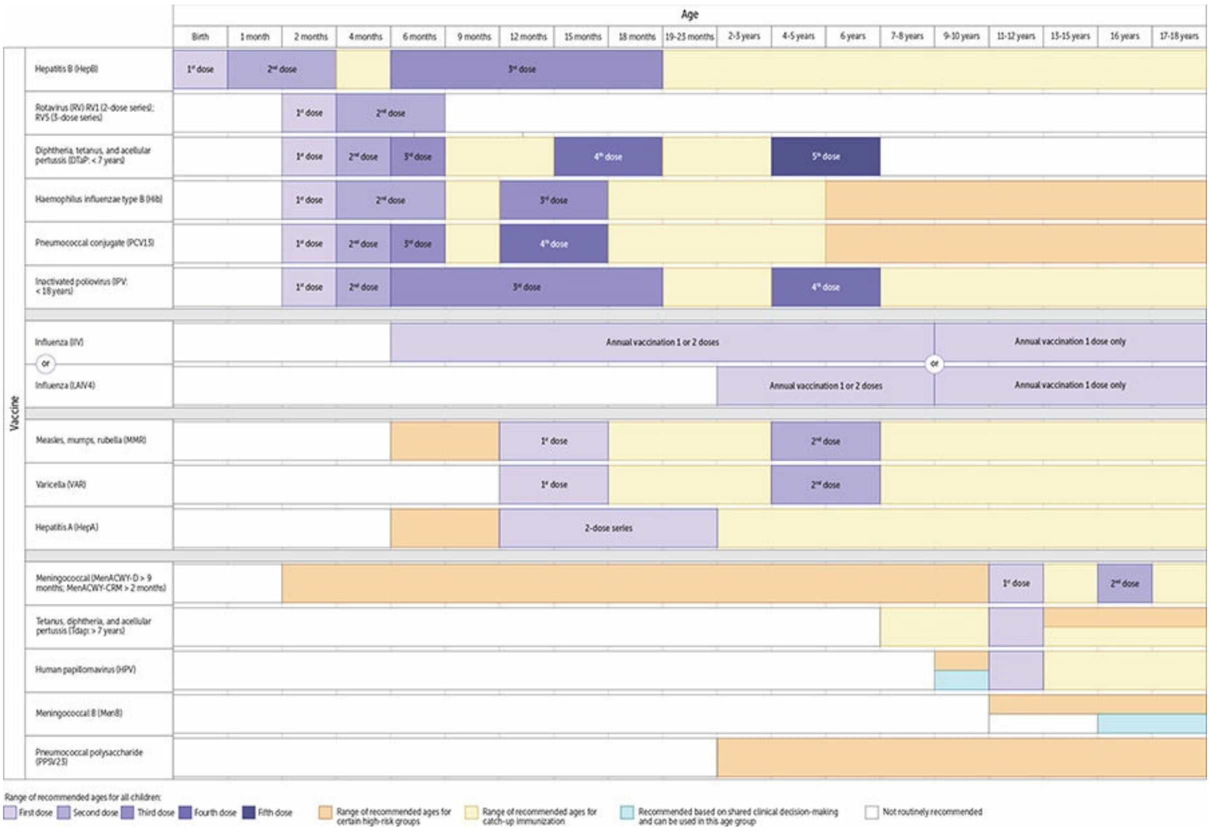
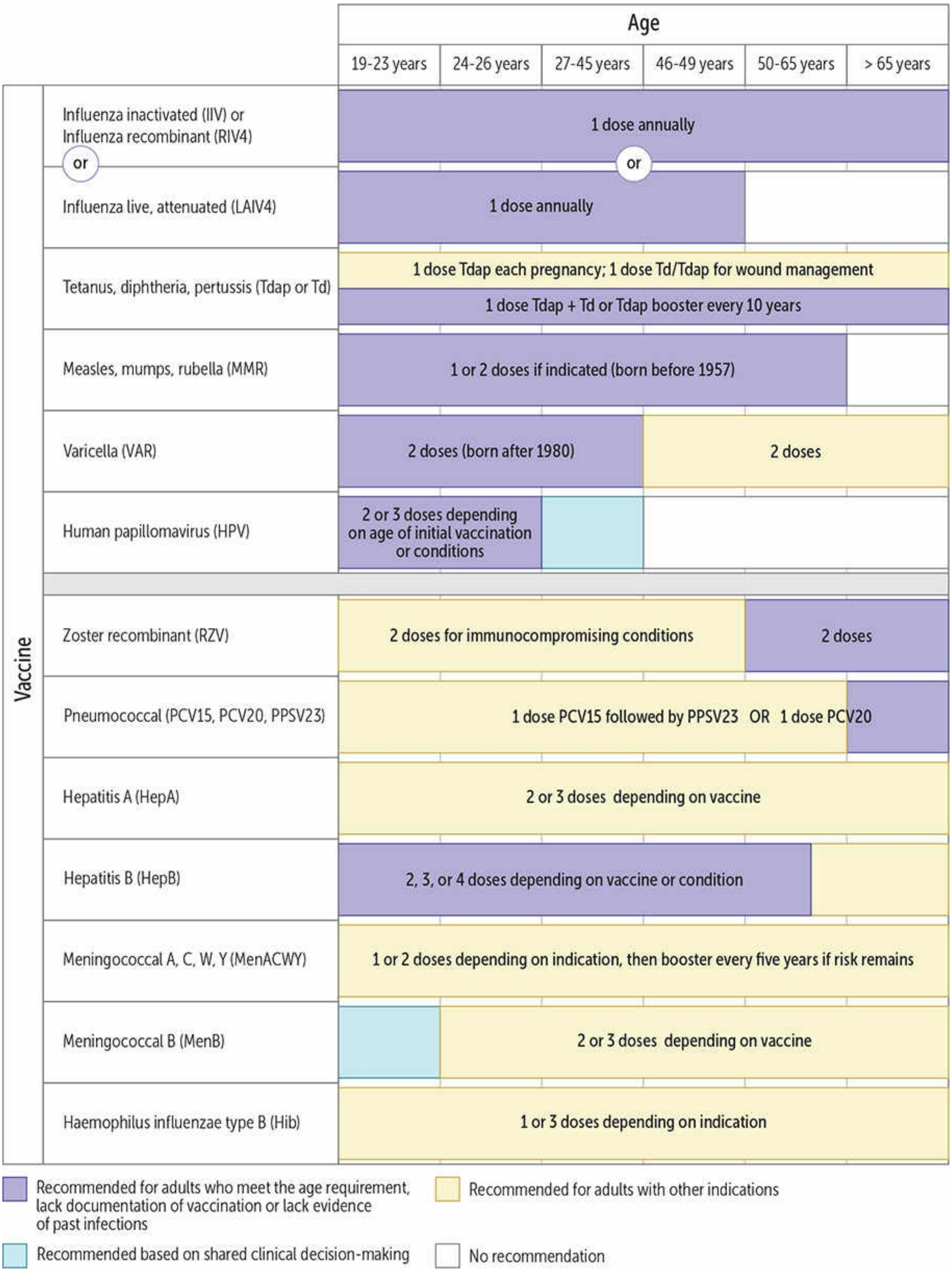


FIGURE 2.4-10. Recommended vaccinations for children 0–18 years of age. (Data collection courtesy of the Centers for Disease Control and Prevention, Atlanta, GA, https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf. Data from 2021.)



Vaccine	19-23 years	24-26 years	27-45 years	46-49 years	50-65 years	> 65 years
Influenza inactivated (IIV) or Influenza recombinant (RIV4)	🟪 1 dose annually	🟪	🟪	🟪	🟪	🟪
or	or					
Influenza live, attenuated (LAIV4)	🟪 1 dose annually	🟪	🟪	🟪	⬜	⬜
Tetanus, diphtheria, pertussis (Tdap or Td)	🟨 1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management 🟪 1 dose Tdap + Td or Tdap booster every 10 years	🟨 🟪	🟨 🟪	🟨 🟪	🟨 🟪	🟨 🟪
Measles, mumps, rubella (MMR)	🟪 1 or 2 doses if indicated (born before 1957)	🟪	🟪	🟪	🟪	⬜
Varicella (VAR)	🟪 2 doses (born after 1980)	🟪	🟪	🟨 2 doses	🟨	🟨
Human papillomavirus (HPV)	🟪 2 or 3 doses depending on age of initial vaccination or conditions	🟪	🟦	⬜	⬜	⬜
Zoster recombinant (RZV)	🟨 2 doses for immunocompromising conditions	🟨	🟨	🟨	🟪 2 doses	🟪
Pneumococcal (PCV15, PCV20, PPSV23)	🟨 1 dose PCV15 followed by PPSV23 OR 1 dose PCV20	🟨	🟨	🟨	🟨	🟪
Hepatitis A (HepA)	🟨 2 or 3 doses depending on vaccine	🟨	🟨	🟨	🟨	🟨
Hepatitis B (HepB)	🟪 2, 3, or 4 doses depending on vaccine or condition	🟪	🟪	🟪	🟪 🟨	🟨
Meningococcal A, C, W, Y (MenACWY)	🟨 1 or 2 doses depending on indication, then booster every five years if risk remains	🟨	🟨	🟨	🟨	🟨
Meningococcal B (MenB)	🟦	🟨 2 or 3 doses depending on vaccine	🟨	🟨	🟨	🟨
Haemophilus influenzae type B (Hib)	🟨 1 or 3 doses depending on indication	🟨	🟨	🟨	🟨	🟨

🟪 Recommended for adults who meet the age requirement, lack documentation of vaccination or lack evidence of past infections

🟨 Recommended for adults with other indications

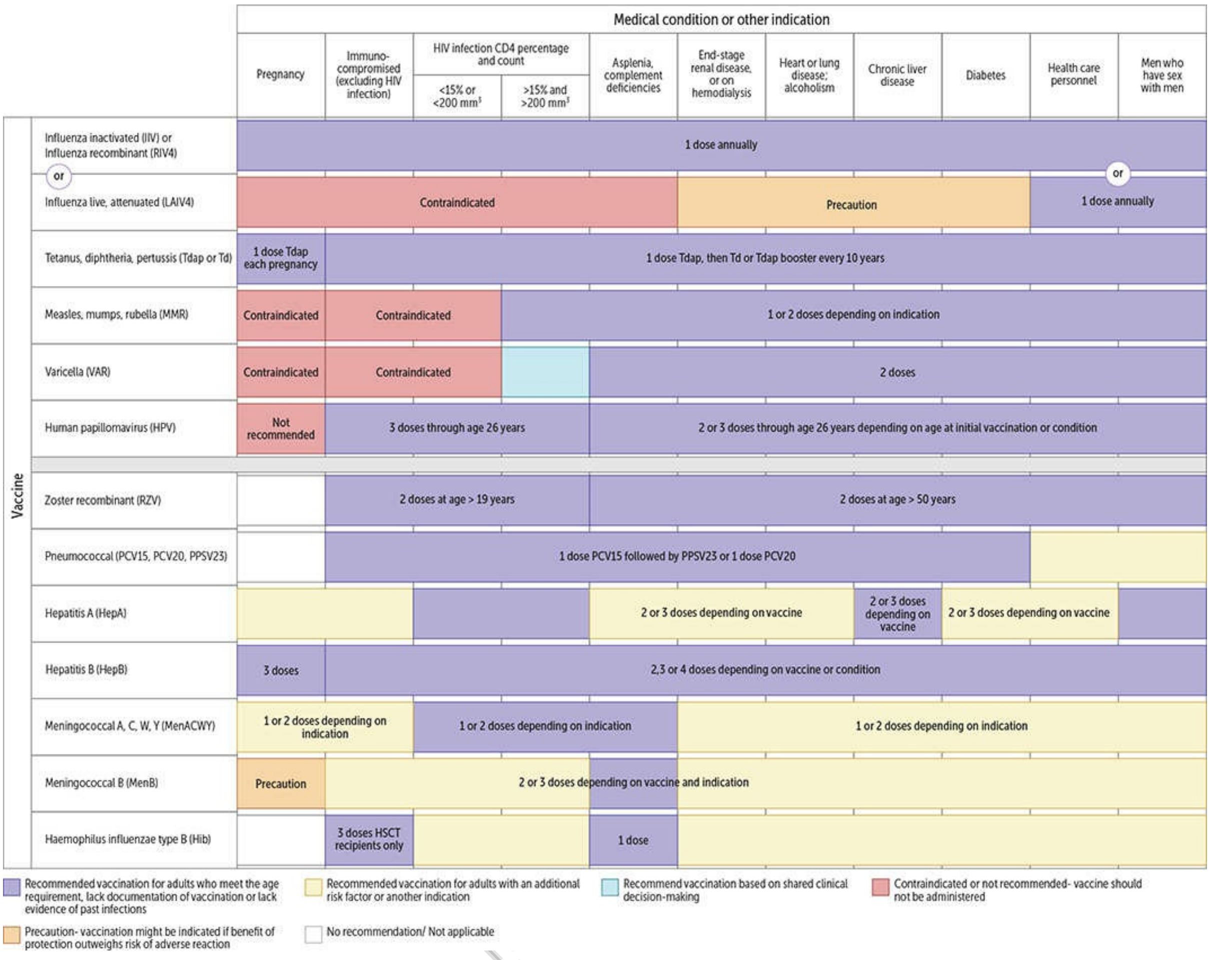
🟦 Recommended based on shared clinical decision-making

⬜ No recommendation

FIGURE 2.4-11. **Recommended vaccinations for adults.** (Data collection courtesy of the Centers for Disease Control and Prevention, Atlanta, GA, https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf. Data from 2021.)

Live vaccines should not be administered to patients with immunosuppression (Fig. 2.4-12). They are also contraindicated in pregnant patients, owing to a theoretical risk for maternal-fetal transmission. A possible exception to this rule can be some asymptomatic

HIV/AIDS patients who may be candidates for the measles, mumps, and rubella (MMR) vaccine.



Vaccine	Medical condition or other indication										
	Pregnancy	Immuno-compromised (excluding HIV infection)	HIV infection CD4 percentage and count		Asplenia, complement deficiencies	End-stage renal disease, or on hemodialysis	Heart or lung disease; alcoholism	Chronic liver disease	Diabetes	Health care personnel	Men who have sex with men
			<15% or <200 mm^3	>15% and >200 mm^3							
Influenza inactivated (IIV) or Influenza recombinant (RIV4)	🟪 1 dose annually	🟪	🟪	🟪	🟪	🟪	🟪	🟪	🟪	🟪	🟪
Influenza live, attenuated (LAIV4)	🟥 Contraindicated	🟥	🟥	🟥	🟥	🟧 Precaution	🟧	🟧	🟧	🟪 1 dose annually	🟪
Tetanus, diphtheria, pertussis (Tdap or Td)	🟪 1 dose Tdap each pregnancy	🟪 1 dose Tdap, then Td or Tdap booster every 10 years	🟪	🟪	🟪	🟪	🟪	🟪	🟪	🟪	🟪
Measles, mumps, rubella (MMR)	🟥 Contraindicated	🟥 Contraindicated	🟥	🟪 1 or 2 doses depending on indication	🟪	🟪	🟪	🟪	🟪	🟪	🟪
Varicella (VAR)	🟥 Contraindicated	🟥 Contraindicated	🟥	🟦	🟪 2 doses	🟪	🟪	🟪	🟪	🟪	🟪
Human papillomavirus (HPV)	🟥 Not recommended	🟪 3 doses through age 26 years	🟪	🟪	🟪 2 or 3 doses through age 26 years depending on age at initial vaccination or condition	🟪	🟪	🟪	🟪	🟪	🟪
Zoster recombinant (RZV)	⬜	🟪 2 doses at age > 19 years	🟪	🟪	🟪 2 doses at age > 50 years	🟪	🟪	🟪	🟪	🟪	🟪
Pneumococcal (PCV15, PCV20, PPSV23)	⬜	🟪 1 dose PCV15 followed by PPSV23 or 1 dose PCV20	🟪	🟪	🟪	🟪	🟪	🟪	🟪	🟨	🟨
Hepatitis A (HepA)	🟨	🟨	🟪	🟪	🟨 2 or 3 doses depending on vaccine	🟨	🟨	🟪 2 or 3 doses depending on vaccine	🟨 2 or 3 doses depending on vaccine	🟨	🟪
Hepatitis B (HepB)	🟪 3 doses	🟪 2,3 or 4 doses depending on vaccine or condition	🟪	🟪	🟪	🟪	🟪	🟪	🟪	🟪	🟪
Meningococcal A, C, W, Y (MenACWY)	🟨 1 or 2 doses depending on indication	🟨	🟪 1 or 2 doses depending on indication	🟪	🟪	🟨 1 or 2 doses depending on indication	🟨	🟨	🟨	🟨	🟨
Meningococcal B (MenB)	🟧 Precaution	🟨 2 or 3 doses depending on vaccine and indication	🟨	🟨	🟪	🟨	🟨	🟨	🟨	🟨	🟨
Haemophilus influenzae type B (Hib)	⬜	🟪 3 doses HSCT recipients only	🟨	🟨	🟪 1 dose	🟨	🟨	🟨	🟨	🟨	🟨

🟪 Recommended vaccination for adults who meet the age requirement, lack documentation of vaccination or lack evidence of past infections

🟨 Recommended vaccination for adults with an additional risk factor or another indication

🟦 Recommend vaccination based on shared clinical decision-making

🟥 Contraindicated or not recommended- vaccine should not be administered

🟧 Precaution- vaccination might be indicated if benefit of protection outweighs risk of adverse reaction

⬜ No recommendation/ Not applicable

FIGURE 2.4-12. **Recommended vaccines for special populations.** (Data collection courtesy of the Centers for Disease Control and Prevention, Atlanta, GA, https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf. Data from 2021.)

COVID-19 VACCINES

At the time of writing this book, in the light of the ongoing pandemic, COVID-19 vaccines are recommended for everyone aged 6 months and older. Number of doses, duration between doses, and need for booster doses vary by manufacturer. Three commonly available vaccines are Pfizer-BioNtech, Moderna, and Janssen/Johnson & Johnson.

SCREENING RECOMMENDATIONS

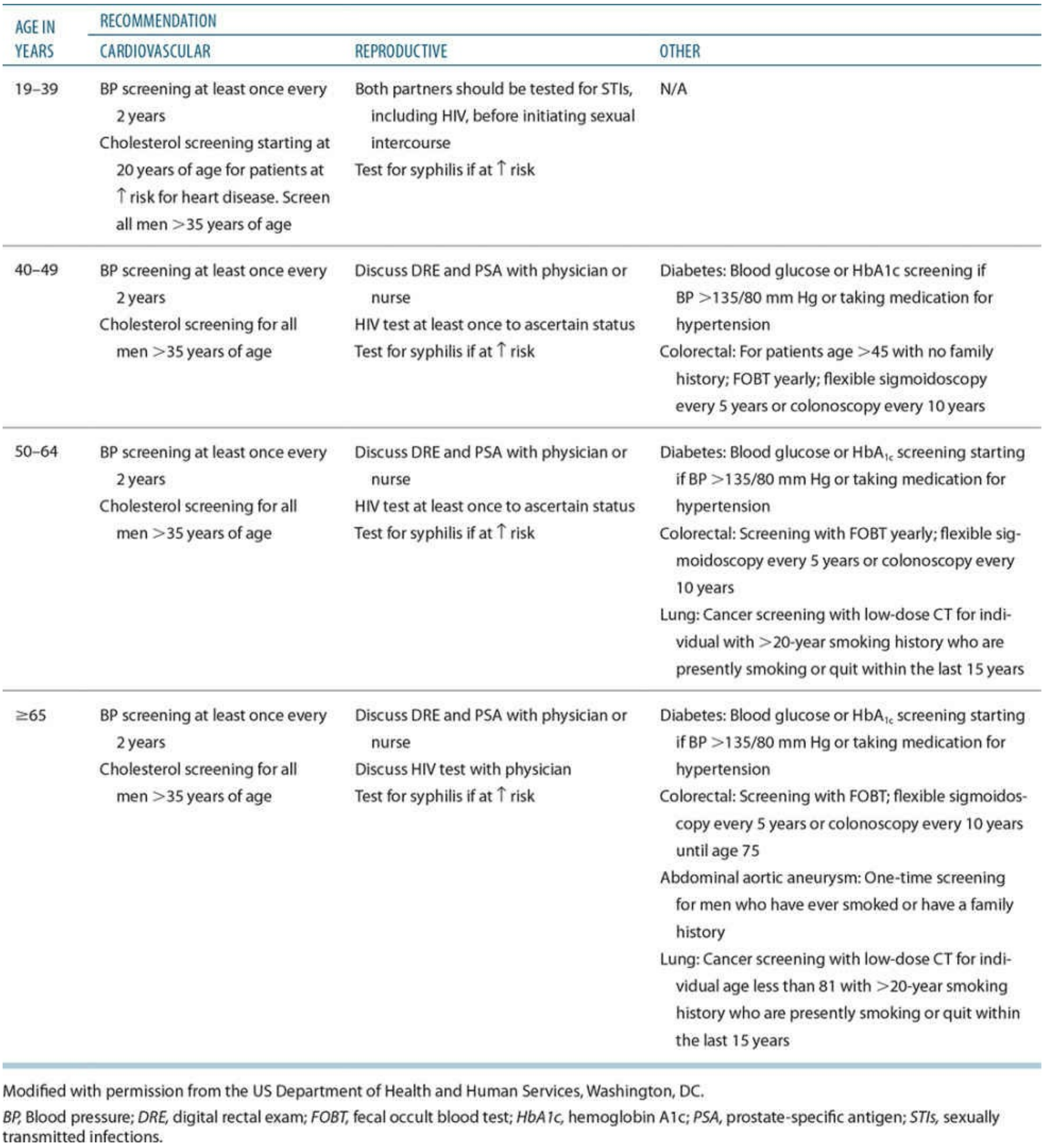
Tables 2.4-4 and 2.4-5 outline recommended healthcare screening measures by gender and age.

TABLE 2.4-4. **Health Screening Recommendations for Women by Age**

AGE IN YEARS	RECOMMENDATION		
	CARDIOVASCULAR	BREAST/REPRODUCTIVE	OTHER
19–39	BP screening at least once every 2 years Cholesterol screening starting at 20 years of age for patients at ↑ risk of heart disease	Pap test every 3 years starting at 21 years of age; co-testing (Pap + HPV) may be done every 5 years starting at 30 years of age Chlamydia test yearly until 24 years of age if sexually active. Women ≥25 years of age should be tested only if there is an ↑ risk HIV test at least once to ascertain status Test for gonorrhea and syphilis if at ↑ risk	Diabetes: Blood glucose or HbA$_{1c}$ screening starting if BP>135/80 mm Hg or taking medication for hypertension
40–49	BP screening at least once every 2 years Cholesterol screening for women >45 years of age	Pap test every 3 years or co-testing every 5 years Pelvic exam yearly; chlamydia test if patient has new or multiple partners HIV test at least once to ascertain status Test for gonorrhea and syphilis if at ↑ risk	Diabetes: Blood glucose or HbA1c screening if BP >135/80 mm Hg or taking medication for hypertension Colorectal: For patients >45 years with no family history; FOBT yearly; flexible sigmoidoscopy every 5 years or colonoscopy every 10 years
50–64	BP screening at least once every 2 years Cholesterol screening for women >45 years of age	Mammogram once every 1–2 years (can start at 40 years of age, if patient chooses) Pap test every 3 years Chlamydia test if patient has new or multiple partners HIV test at least once to ascertain status Test for gonorrhea and syphilis if at ↑ risk	Diabetes: Blood glucose or HbA1c screening if BP >135/80 mm Hg or taking medication for hypertension Bone: DEXA scan can be done in patients with other osteoporosis risk factors Colorectal: FOBT yearly; flexible sigmoidoscopy every 5 years or colonoscopy every 10 years
≥65	BP screening at least once every 2 years Cholesterol screening for women >45 years of age	Mammogram once every 1–2 years until 75 years of age Discuss Pap test with physician or nurse Chlamydia test if patient has new or multiple partners Discuss HIV test with physician or nurse Test for gonorrhea and syphilis if at ↑ risk	Diabetes: Blood glucose or HbA1c screening if blood pressure higher than 135/80 or taking medication for hypertension Bone: DEXA scan at least once Colorectal: Screening with FOBT, sigmoidoscopy, or colonoscopy every 10 years until 75 years of age

Modified with permission from the U.S. Department of Health and Human Services, Washington, DC.
BP, Blood pressure; *DEXA,* dual-energy x-ray absorptiometry; *FOBT,* fecal occult blood test; *HbA1c,* hemoglobin A1c; *HPV,* human papillomavirus.

TABLE 2.4-5. **Health Screening Recommendations for Men by Age**



AGE IN YEARS	RECOMMENDATION		
	CARDIOVASCULAR	REPRODUCTIVE	OTHER
19–39	BP screening at least once every 2 years Cholesterol screening starting at 20 years of age for patients at ↑ risk for heart disease. Screen all men >35 years of age	Both partners should be tested for STIs, including HIV, before initiating sexual intercourse Test for syphilis if at ↑ risk	N/A
40–49	BP screening at least once every 2 years Cholesterol screening for all men >35 years of age	Discuss DRE and PSA with physician or nurse HIV test at least once to ascertain status Test for syphilis if at ↑ risk	Diabetes: Blood glucose or HbA1c screening if BP >135/80 mm Hg or taking medication for hypertension Colorectal: For patients age >45 with no family history; FOBT yearly; flexible sigmoidoscopy every 5 years or colonoscopy every 10 years
50–64	BP screening at least once every 2 years Cholesterol screening for all men >35 years of age	Discuss DRE and PSA with physician or nurse HIV test at least once to ascertain status Test for syphilis if at ↑ risk	Diabetes: Blood glucose or HbA_{1c} screening starting if BP >135/80 mm Hg or taking medication for hypertension Colorectal: Screening with FOBT yearly; flexible sigmoidoscopy every 5 years or colonoscopy every 10 years Lung: Cancer screening with low-dose CT for individual with >20-year smoking history who are presently smoking or quit within the last 15 years
≥65	BP screening at least once every 2 years Cholesterol screening for all men >35 years of age	Discuss DRE and PSA with physician or nurse Discuss HIV test with physician Test for syphilis if at ↑ risk	Diabetes: Blood glucose or HbA_{1c} screening starting if BP >135/80 mm Hg or taking medication for hypertension Colorectal: Screening with FOBT; flexible sigmoidoscopy every 5 years or colonoscopy every 10 years until age 75 Abdominal aortic aneurysm: One-time screening for men who have ever smoked or have a family history Lung: Cancer screening with low-dose CT for individual age less than 81 with >20-year smoking history who are presently smoking or quit within the last 15 years

Modified with permission from the US Department of Health and Human Services, Washington, DC.

BP, Blood pressure; *DRE,* digital rectal exam; *FOBT,* fecal occult blood test; *HbA1c,* hemoglobin A1c; *PSA,* prostate-specific antigen; *STIs,* sexually transmitted infections.

REPORTABLE DISEASES

By law, disease reporting is mandated at the state level, and the list of diseases that must be reported to public health authorities varies slightly by state. The Centers for Disease Control and Prevention (CDC) has a list of nationally notifiable diseases that states voluntarily report. These diseases include but are not limited to those listed in Table 2.4-6.

TABLE 2.4-6. Common Reportable Diseases

DISEASE CATEGORY	EXAMPLES
STIs	HIV/AIDS, syphilis, gonorrhea, chlamydia, chancroid, HCV
Tick-borne disease	Lyme disease, ehrlichiosis, Rocky Mountain spotted fever
Potential bioweapons	Anthrax, smallpox, plague
Vaccine-preventable disease	Diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, varicella, HAV, HBV, *H influenzae* (invasive), meningococcal disease
Water-/food-borne disease	Cholera, giardiasis, *Legionella*, listeriosis, botulism, shigellosis, Shiga toxin–producing *Escherichia coli*, salmonellosis, trichinellosis, typhoid
Zoonoses	Tularemia, psittacosis, brucellosis, rabies
Miscellaneous	TB, leprosy, toxic shock syndrome, SARS, COVID-19, West Nile virus, VRSA, coccidioidomycosis, cryptosporidiosis; MRSA is reportable in several states

HAV, Hepatitis A virus; *HBV,* hepatitis B virus; *MRSA,* methicillin-resistant *Staphylococcus aureus; SARS,* severe acute respiratory syndrome; *STIs,* sexually transmitted infections; *TB,* tuberculosis; *VRSA,* vancomycin-resistant *S aureus.*

HIGH-YIELD FACTS IN

HEALTH SYSTEMS SCIENCE

Health System Delivery
- HEALTH INSURANCE PLANS
- MEDICARE AND MEDICAID
- PALLIATIVE CARE

Communication
- PATIENT-CENTERED, EVIDENCE-BASED INTERVIEWING
- EFFORTS TO ESTABLISH RAPPORT
- CHALLENGING CONVERSATIONS
- GENDER- AND SEXUALITY-INCLUSIVE HISTORY TAKING
- CULTURALLY INCLUSIVE HISTORY TAKING
- MOTIVATIONAL INTERVIEWING
- COMMUNICATING WITH PATIENTS WITH DISABILITIES
- INTERPRETERS
- BEHAVIORAL COUNSELING

Patient Safety and Quality
- SAFETY CULTURE
- PDSA CYCLE
- SWISS CHEESE MODEL
- MEASURING QUALITY OUTCOMES
- ERRORS IN HEALTHCARE
- HEALTHCARE WORKER BURNOUT AND FATIGUE
- ANALYZING MEDICAL ERRORS

Ethics and Legal Issues
- GENERAL/CORE PRINCIPLES
- DOCTOR-PATIENT PROFESSIONAL RELATIONSHIP
- DOCTOR-PATIENT SEXUAL RELATIONSHIP

Competence and Decision-Making Capacity
- COMPETENCE
- DECISION-MAKING CAPACITY
- INFORMED CONSENT

End-of-Life Issues
- ADVANCE DIRECTIVES
- SURROGATE DECISION MAKING
- WITHDRAWAL OF LIFE-SUSTAINING TREATMENT
- EUTHANASIA AND CLINICIAN-ASSISTED SUICIDE
- HOSPICE CARE
- FUTILE TREATMENT

Complementary and Alternative Medicine Therapy

- Disclosure
  - FULL DISCLOSURE
  - SETTING FOR DELIVERING NEWS
- Confidentiality
- Clinical Research
  - CORE PRINCIPLES OF CLINICAL RESEARCH
  - ETHICAL CONCERNS
- Conflict of Interest
  - GIFTS FROM PATIENTS
  - GIFTS FROM DRUG COMPANIES
- Malpractice
  - DEFINING MALPRACTICE
  - IMPAIRED PRACTICING CLINICIANS

HEALTH SYSTEM DELIVERY

HEALTH INSURANCE PLANS

Patients may receive insurance from various providers that reimburse the insured patients based on the services they utilize. These services may provide payment to the clinician or organization in one of the following ways:

- **Bundled payment:** Organization receives set amount per service, regardless of ultimate cost, with the received amount divided among all providers and facilities involved.
- **Capitation:** Clinicians receive a set amount per patient per period regardless of the healthcare utilization. This is usually provided by health maintenance organizations.
- **Fee-for-service insurance:** The patient or insurer pays for each individual service.
- **Discounted fee-for-service insurance:** The patient or insurer pays for each utilized service at a discounted rate predetermined by providers and payers. This service is mostly used by preferred provider organizations.
- **Global payment:** The patient or insurer pays for all expenses for a single incident of care, with a single payment once the service is used. For example, payment for elective surgeries may cover the cost of the surgery and the necessary preoperative and postoperative visits.

MEDICARE AND MEDICAID

Many patients may have Medicare or Medicaid enrollment, and this may affect the services they choose to utilize (Table 2.5-1).

TABLE 2.5-1. Medicare vs Medicaid

	MEDICARE	MEDICAID
Administrating body	Federal	Federal and state
Type of program	Insurance	Assistance
Eligibility	Patients ≥65 years of age, younger patients with disability, patients undergoing dialysis	Low-income patient of any age
Bill payment	Trust funds	Patients do not pay any part of expenses
Copays and deductibles	Small monthly premiums for nonhospital coverage	Small copayment (in some cases)
Coverage	Part A: Hospital admissions including hospice, skilled nursing Part B: Basic medical bills (eg, clinician fees, diagnostic testing) Part C: Delivered by approved private companies (delivers all services of parts A and B) Part D: Prescription drugs	Basic healthcare and prescription drug costs, long-term care, medical equipment, prescription glasses, dental care, and more

PALLIATIVE CARE

This is an approach to improve the quality of life for patients experiencing life-threatening illness and for their families. The goals of palliative care are to minimize suffering and to provide care that is consistent with the patient's values. This includes addressing symptoms such as pain, dyspnea, or any other physical symptoms; psychological distress; and social issues. A palliative care team also provides support to families during the patient's illness and their family's subsequent bereavement. Care is provided via a team approach (eg, clinicians, nurses, social workers) to support patients and their caregivers. The palliative care approach has five stages:

1. **Stable:** A treatment plan is created, and medical interventions are placed to control symptoms and enhance quality of life.
2. **Unstable:** Existing symptoms worsen, or patients may have unexpected symptoms, and the care of plan is changed. This stage requires provision of mental, emotional, and spiritual support.
3. **Deteriorating:** Overall health and body functions of the patient gradually decline, leading to mental and physical distress in the patient and for their family. Emotional support is key during this stage.
4. **Terminal:** The patient may become bedridden, have loss of appetite, have difficulty in swallowing, and may require daily medical interventions. A hospital setting may be needed for further care provision.
5. **Bereavement:** This is the stage where the patient has died. The care plan focuses on caring for the patient's loved ones and addressing their emotional needs, including connection with specific support groups; spiritual support, eg, via a pastor, priest, or rabbi; and psychosocial support to tackle grief, loss, and adjustment.

When the prognosis for the patient is less than 6 months, or when life-prolonging treatment is no longer beneficial, the patient may be referred to end-of-life care or hospice care.

COMMUNICATION

PATIENT-CENTERED, EVIDENCE-BASED INTERVIEWING

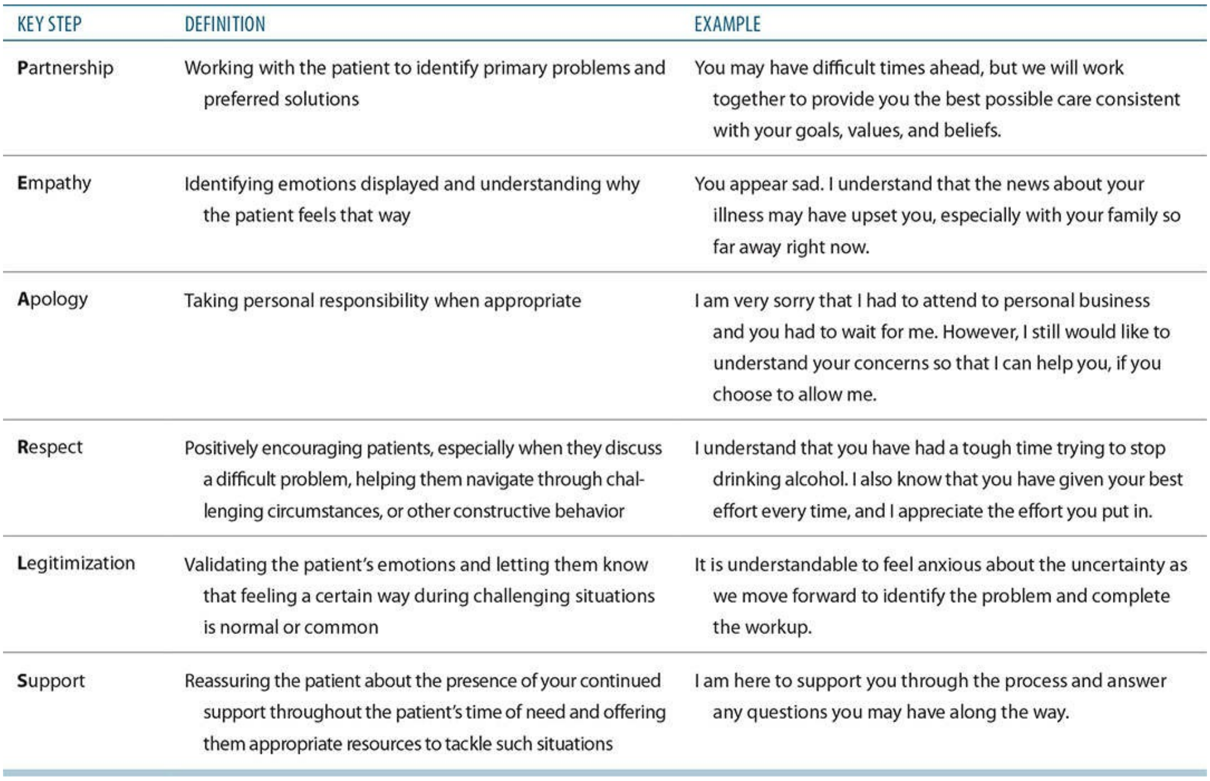
There are certain key ways to make a patient feel comfortable being interviewed about their medical history. Following these steps can help obtain a reliable history. These steps are outlined here:

- **Setting the stage:** Welcome the patient and use the patient's preferred name or pronouns to address them directly. Introduce yourself and identify your specific role. Ensure privacy and comfort for the patient. When patients are accompanied by a caregiver, let them introduce themselves and clarify with the patient if they would want their caregiver to be included in the discussion.
- **Agenda of interview:** Indicate the time available and obtain a list of issues the patient wants to discuss. Let the patient understand how the interview will proceed, and summarize the agenda for that interview.
- **Nonfocused expression/reflection:** Always start with open-ended questions or requests and use nonverbal cues (eg, patient gestures) to obtain more information.
- **Focused expression/validation:** Elicit further history with a focus on description of symptoms, with perspective of impact on the patient's personal, psychosocial, and emotional contexts. Identify the patient's beliefs and attributions, while addressing feelings and emotions (**N**aming, **U**nderstanding, **R**especting, **S**upporting, **E**xploring, or the **NURSE** technique).
- **Recapitulate:** Check accuracy by providing a brief summary of what has been dealt with and what needs further input.
- **Facilitation:** Encourage the patient to speak freely and ask questions throughout the interview.
  - **Open-ended skills:** Can be nonfocusing techniques like silence (to allow patient to speak), nonverbal encouragement, and prompting the patient to continue with their story, or focusing techniques like echoing (repeating what the patient just said and asking if this is correct), requesting, and summarizing.
  - **Emotion-seeking skills:** Ask directly how this condition or situation affects the patient's emotions. Indirect assessment can include impact of condition on life, beliefs the patient has about their problems, and any triggers that relate to the problem.
  - **Empathy:** **N**ame, **U**nderstand, **R**espect, **S**upport, **E**xplore.

EFFORTS TO ESTABLISH RAPPORT

Establishing rapport may be the most difficult part of the medical interview, but there are certain steps to follow for this process as well. Establishing rapport can be done by either the PEARLS model (see Table 2.5-2) or the Ask-Tell-Ask model.

TABLE 2.5-2. **PEARLS Model of Establishing Rapport**



KEY STEP	DEFINITION	EXAMPLE
Partnership	Working with the patient to identify primary problems and preferred solutions	You may have difficult times ahead, but we will work together to provide you the best possible care consistent with your goals, values, and beliefs.
Empathy	Identifying emotions displayed and understanding why the patient feels that way	You appear sad. I understand that the news about your illness may have upset you, especially with your family so far away right now.
Apology	Taking personal responsibility when appropriate	I am very sorry that I had to attend to personal business and you had to wait for me. However, I still would like to understand your concerns so that I can help you, if you choose to allow me.
Respect	Positively encouraging patients, especially when they discuss a difficult problem, helping them navigate through challenging circumstances, or other constructive behavior	I understand that you have had a tough time trying to stop drinking alcohol. I also know that you have given your best effort every time, and I appreciate the effort you put in.
Legitimization	Validating the patient's emotions and letting them know that feeling a certain way during challenging situations is normal or common	It is understandable to feel anxious about the uncertainty as we move forward to identify the problem and complete the workup.
Support	Reassuring the patient about the presence of your continued support throughout the patient's time of need and offering them appropriate resources to tackle such situations	I am here to support you through the process and answer any questions you may have along the way.

CHALLENGING CONVERSATIONS

When delivering challenging or difficult-to-break news to patients, one should think about the following (SPIKES):

- **Setting:** As with effective history taking, one should ensure a private environment free from distractions when presenting news to the patient.
- **Perception:** Before proceeding with delivering the news, always ask first what the patient thinks about their illness and what their understanding of their current state of health is.
- **Invitation:** Ask the patient if they have any queries they would like answered and the amount of information that they would like to obtain from the clinician before delivering the news.
- **Knowledge:** Educate the patient about the news in small pieces, allowing time for them to process. Assess the patient's understanding of the news step by step.
- **Emotions:** Acknowledge that the patient responds to the news in a certain way and acknowledge their emotions. When dealing with patients' emotions, always be empathetic to their responses and listen to them without interrupting.
- **Strategy:** Once the patient feels ready to further discuss treatment options or prognosis and goals of care, offer them an agenda about how to proceed, and schedule their appointments around these agendas.

GENDER- AND SEXUALITY-INCLUSIVE HISTORY TAKING

When interviewing the patient, always take into consideration the following points:

- Avoid making assumptions about a patient's sexual orientation, gender identity, gender expression, or sexual behavior without first asking the patient about these. If gender or sexuality is not relevant for the presenting illness, do not bring it up.

- Note that the patient may identify as a different gender than the sex assigned to them at birth.
- Try to use gender-neutral terms (eg, partner or spouse) rather than assuming their gender.
- Always reassure the patient that whatever they share is confidential and even if they are not open about their sexual orientation or gender identity, this information will not be revealed to anyone else without the patient’s prior permission or request.

CULTURALLY INCLUSIVE HISTORY TAKING

As stressed earlier, patients have their own cultures and specific goals, values, or beliefs and may not accept the treatment plan proposed for them. Always note the following points when interviewing patients:

- Try to think about the illness from the patient’s perspective.
- Try to understand what factors in the patient’s cultures or background (or even some past experiences) influences certain decisions they make.
- Also note how their culture would affect future decisions for treatment.

For example, note that patients who belong to the Jehovah’s Witnesses may refuse lifesaving blood transfusion for themselves (if adult and competent), but they cannot do the same if their child (who is below the legal age and not an emancipated minor) because this amounts to child abuse.

KEY FACT

When treatment can save a child’s life, or if the outcome of treatment is a normal life with a reasonably good quality of life, or if the medical community is in agreement about the course of action and if the parent is refusing to grant consent to proceed, the healthcare decisions for that child can be taken over by the State.

MOTIVATIONAL INTERVIEWING

Make sure to counsel the patient on every visit about improving their behavior to help treat their illness if these behaviors affect them directly or indirectly. For example, if a patient smokes, mention smoking cessation at every visit. When the patient notes a desire to change their behavior, document this step and encourage them. If the patient is not expressing such a desire, assess any barriers that may lead to difficulty in changing these behaviors. Expressing a desire to change their behavior is the first step to changing the behavior itself. Once a patient has expressed a desire to change, set goals for the patients to meet. These goals should be Specific, Measurable, Achievable, Relevant, and Time bound (SMART).

COMMUNICATING WITH PATIENTS WITH DISABILITIES

When interviewing a patient who has a disability or disabilities, speak directly to the patient and ask them how they identify themselves: person first (ie, a person with a disability) or identity first (ie, a disabled person). Obtain additional information from caregivers when appropriate. Do not assume that these patients cannot complete a certain task; rather, ask them if they require assistance.

- For patients with speech difficulties, provide extra time for an interview.
- For patients with cognitive impairment, use specific language and ask simple, direct questions.
- For patients who are hard of hearing ask them about their preferred mode of communication. Consider using an interpreter when necessary.
- Also, do not bring up a disability if it is not relevant to the presenting illness. Do not skip portions of the physical examination even if the disability makes the exam challenging.

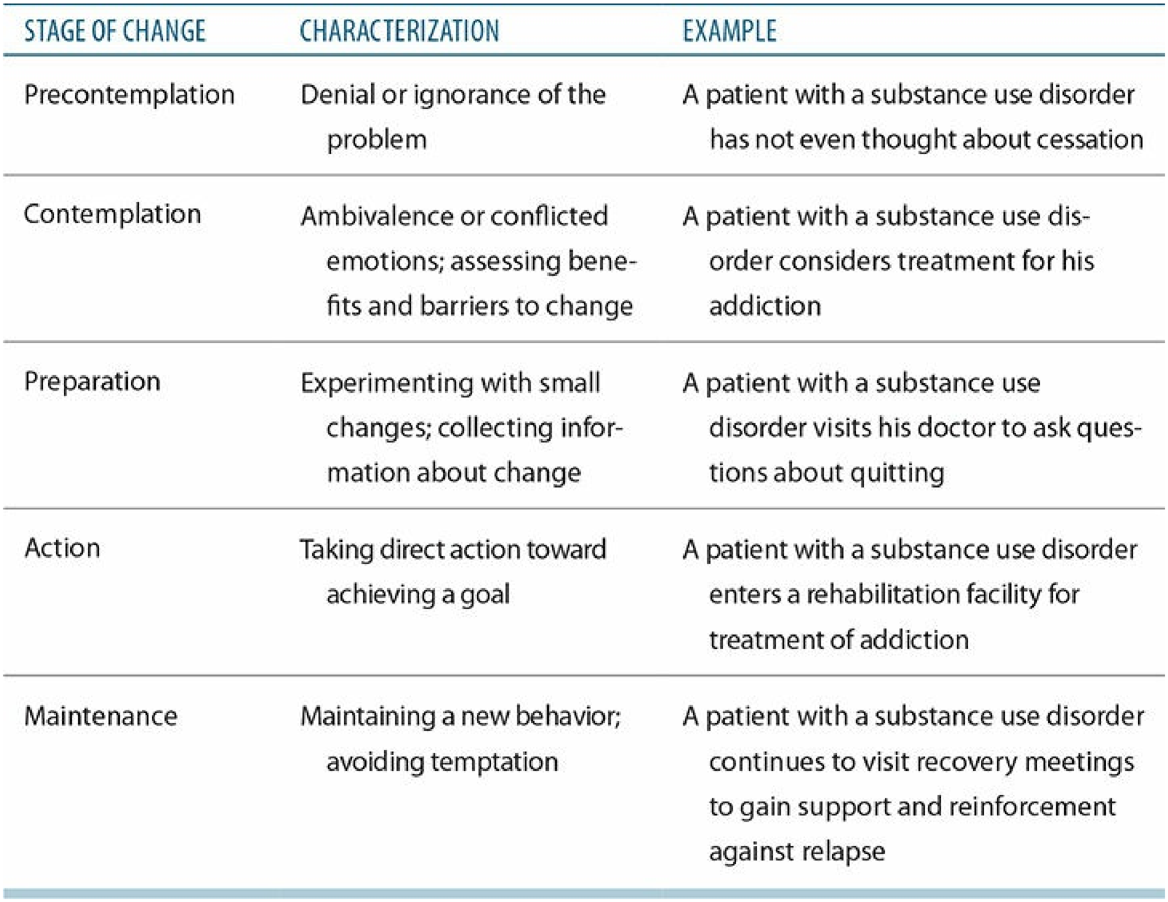
INTERPRETERS

When patients who do not speak English or have difficulty in conversing in the language, always use a professionally trained medical interpreter for communication unless the clinician is conversationally fluent in the patient’s preferred language. If professional interpreters are unavailable or if you are working with the patient outside service hours, a telephone or video call may provide the same service. If the patient prefers to use a family member for interpretation, this should be recorded in the chart. In emergencies, facilitate communication using any tools available (eg, friends, family, interpreter apps) even though this may not be standard procedure otherwise.

BEHAVIORAL COUNSELING

When offering counsel, clinicians should tailor their education and suggestions to the individual patient, as well as to their stage of change (see Table 2.5-3 and Fig. 2.5-1).

TABLE 2.5-3. Stages of Change in Behavioral Counseling



STAGE OF CHANGE	CHARACTERIZATION	EXAMPLE
Precontemplation	Denial or ignorance of the problem	A patient with a substance use disorder has not even thought about cessation
Contemplation	Ambivalence or conflicted emotions; assessing benefits and barriers to change	A patient with a substance use disorder considers treatment for his addiction
Preparation	Experimenting with small changes; collecting information about change	A patient with a substance use disorder visits his doctor to ask questions about quitting
Action	Taking direct action toward achieving a goal	A patient with a substance use disorder enters a rehabilitation facility for treatment of addiction
Maintenance	Maintaining a new behavior; avoiding temptation	A patient with a substance use disorder continues to visit recovery meetings to gain support and reinforcement against relapse

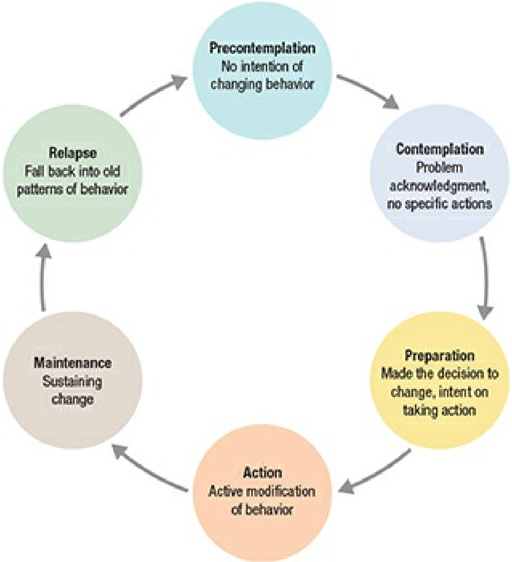

Precontemplation
No intention of changing behavior
Contemplation
Problem acknowledgment, no specific actions
Preparation
Made the decision to change, intent on taking action
Action
Active modification of behavior
Maintenance
Sustaining change
Relapse
Fall back into old patterns of behavior

FIGURE 2.5-1. **Stages of change model.** (Reproduced with permission from USMLE-Rx.com.)

PATIENT SAFETY AND QUALITY

SAFETY CULTURE

This is a part of an organization’s culture, which is a collection of the beliefs, perceptions, and values that the employees share in relation to risks within the healthcare sector. To note, the Institute of Medicine noted that the “focus must shift from blaming individuals for past errors to a focus on preventing future errors by designing safety into the system.” So, patient safety includes the process of amelioration, avoidance, and prevention of adverse injuries or outcomes that arise because of the healthcare process.

PDSA CYCLE

The PDSA cycle involves four key processes (Plan, Do, Study, Act) that help identify possible deficiencies in provisions of care, which when changed, can affect healthcare delivery and improve patient safety. This is a continuous cycle, and it requires reassessment of strategies after implementation of a plan for a set time period (see Fig. 2.5-2).

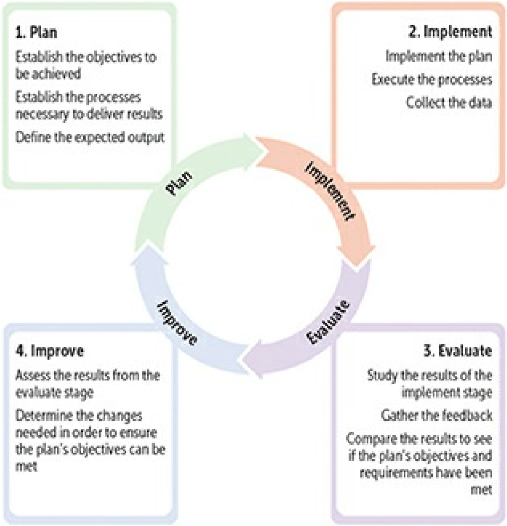

1. Plan
Establish the objectives to be achieved
Establish the processes necessary to deliver results
Define the expected output
2. Implement
Implement the plan
Execute the processes
Collect the data
Plan
Implement
Evaluate
Improve
4. Improve
Assess the results from the evaluate stage
Determine the changes needed in order to ensure the plan's objectives can be met
3. Evaluate
Study the results of the implement stage
Gather the feedback
Compare the results to see if the plan's objectives and requirements have been met

FIGURE 2.5-2. **PDSA cycle.** (Reproduced with permission from USMLE-Rx.com.)

SWISS CHEESE MODEL

This is a model of risk assessment that focuses on systems and conditions that may align to lead to an adverse event. The Swiss cheese model tries to mitigate such threats at various levels. However, despite provisions of multiple safeguards, an error may occur and lead to harm to the patient when the "holes in the cheese line up" (see Fig. 2.5-3). During a root cause analysis, the goal is to understand how the adverse event occurred, including by understanding how each of these safeguards may have failed. In doing so, efforts to add additional safeguards or revise prior safeguards can help minimize future adverse events.

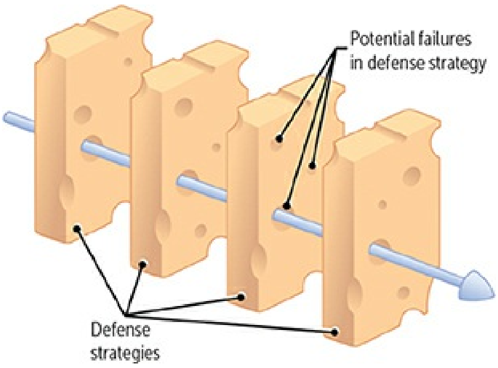

Potential failures in defense strategy
Defense strategies

FIGURE 2.5-3. **Swiss cheese model of safeguarding delivery of care.** (Reproduced with permission from USMLE-Rx.com.)

MEASURING QUALITY OUTCOMES

Delivery of quality healthcare can be assessed by various processes that may evaluate the structure, process, outcome, and balance of any healthcare system:

- **Structural:** Assessment of physical equipment, resources, and facilities. Example: Machine used to evaluate the potassium levels of patients.
- **Process:** Assessment of function of the healthcare system as planned. Example: Number of patients undergoing dialysis utilizing the said function.
- **Outcome:** Measurement of the impact of the healthcare measure on patients. Example: Average levels of potassium of patients undergoing dialysis.

- **Balancing:** Assessment of impact on other systems or outcomes. Example: Average drop in levels of potassium of patients who underwent dialysis compared with the initial levels.

ERRORS IN HEALTHCARE

Although a clinician may have no intention to bring about harm to the patient, certain processes may align to bring about errors in healthcare delivery (see Table 2.5-4). These are called adverse events (errors in medical or surgical treatment that can potentially lead to patient harm, rather than as an impact of the patient's previous underlying medical condition). The outcome of such events may be unintended injury to the patient, prolonged hospitalization, or even disability.

TABLE 2.5-4. Errors in Healthcare Delivery

TYPE OF ERROR	DESCRIPTION	IMPACT
Active error	At the level of the front-line operator	Immediate impact (eg, wrong intravenous [IV] dose or illegible handwriting on orders).
Latent error	Indirect processes that affect patient care	Accident waiting to happen (eg, different types of IV pumps used within the same hospital).
Never event	Errors that should never happen	Major error that should never occur (eg, wrong foot amputated).
Near miss	Event that could have led to harm but did not	Intervention by someone or something that led to prevention but should have not happened (eg, medication interactions that may be recognized by the pharmacist and corrected or cancelled).
Medical error	Failure to complete the intended plan of action or implementation of wrong plan to achieve treatment goal	Deviation from process of care. May lead to unintended consequence (eg, administration of a wrong dose of medication when a full stop was interpreted as a comma, ie, 100 U insulin when the order stated 10.0 U).
Negligence	Failure to meet expected standard of care	May lead to direct harm to the patient (eg, missing the pathology report of a cancer diagnosis).
Sentinel event	Any unexpected occurrence involving death or serious harm to the patient or the risk thereof	When repeated, there is a significant chance for a serious adverse outcome (eg, using the same bronchoscope for several patients and not cleaning between the procedures due to miscommunication between staff).

HEALTHCARE WORKER BURNOUT AND FATIGUE

The leading causes of errors in provision of care include healthcare worker burnout and fatigue. Burnout may occur with prolonged, excessive stress and lead to reduced professional efficacy. Burnout can be due to intrinsic demands of the job, individual susceptibility, and poor work organization. Deprivation of sleep or rest can lead to cognitive impairment and lead to medical errors. This can be minimized by:

- Setting clear and consistent goals for the staff
- Providing training to increase coping strategies, increase role effectiveness, and nurture better conflict resolution strategies
- Encouraging support groups and resource exchange networks
- Organizing workload and working time, with regular breaks and flexible schedules
- Providing accommodation for health workers during emergency operations with access to food services, sanitary facilities, and adequate recreational opportunities

ANALYZING MEDICAL ERRORS

When analyzing medical errors, two different models may be commonly used: (1) root cause analysis and (2) failure mode and effects analysis. The root cause approach is applied after a system failure to find out what went wrong, whereas the failure mode and effects analysis is applied before an error occurs to prevent failure.

- **Root cause analysis:** Typically evaluates sentinel events to decrease the odds of repeating the same event. This process uses records and participant interviews (eg, five whys approach, fishbone diagrams, cause-effect diagrams, process maps) to identify the underlying cause of error.
- **Failure mode and effects analysis:** Concludes that errors will occur even if healthcare professionals are careful. This process helps build redundancies that act as safety nets to trap errors. The process uses inductive reasoning to identify all the ways a system might fail and prioritizes them by their probability of occurrence and impact on patients.

ETHICS AND LEGAL ISSUES

GENERAL/CORE PRINCIPLES

- **Respect for autonomy:** This is absolute. Clinicians are obligated to respect patients as individuals and to honor their preferences.
  - Example: A pregnant patient has the right to refuse a cesarean section despite potential risk to the fetus. This is called the principle of maternal autonomy—as long as the mother has capacity, she has ultimate rights over her unborn child (in the United States), as the fetus is considered a part of the mother.

KEY FACT

In some cases (eg, psychiatric illness, grave disability), the Baker Act allows for the involuntary hospitalization of patients against their will if they are deemed a threat to themselves or others and are neglectful.

- **Beneficence:** Clinicians have a responsibility to act in the patient's best interest. Respect for patient autonomy may conflict with beneficence. In general, if a patient is mentally competent, respect for patient autonomy supersedes beneficence even if the clinician believes the patient is not acting in their best interest.
  - Example: The clinician has a responsibility to recommend a lifesaving transfusion to a Jehovah's Witness (beneficence) and respect the patient's autonomy if they should refuse. However, when a parent who is a Jehovah's Witness refuses emergency medical treatment for their child (claiming the same status for the child), the clinician is not obliged to agree with the parent, but must instead provide the necessary treatment to save the life of the child (beneficence outweighs autonomy).
- **Nonmaleficence:** "Do no harm." All medical interventions involve benefits and risks, and clinicians should generally only recommend treatments for which the likely benefits outweigh the known risks. Also, it should be made clear to the patient the consequences of refusing treatment if they were to choose so. This category includes most medical and

surgical interventions.
  - Example: A surgeon declines to perform a procedure because they think the patient will die intraoperatively.
- **Justice:** Healthcare is a scarce resource. Fairness and equality in distribution and delivery of healthcare are ongoing challenges for health policy and in the clinical arena.
  - Example: A state designs a program for homeless people.

DOCTOR-PATIENT PROFESSIONAL RELATIONSHIP

- The doctor-patient relationship is a voluntary relationship. It occurs when the patient agrees to seek medical attention with a specific doctor and when the doctor agrees to care for the patient.
- In a hospital setting, emergency management should be provided to all patients.
  - In the absence of an emergent condition, the clinician is under no legal obligation to accept caring for patients.
  - Example: If a pregnant patient is seeking to get an abortion, the clinician is under no *legal* obligation to perform the procedure if that goes against their moral standards.
- To end a doctor-patient relationship, the doctor should allow patients to have adequate time to find an alternative clinician.

KEY FACT

Clinicians are not obligated to accept every person coming to them as a patient. Furthermore, clinicians have the right to end a doctor-patient relationship but must give the patient the resources and time to find another clinician.

DOCTOR-PATIENT SEXUAL RELATIONSHIP

- Sexual contact between clinicians and their patients is always inappropriate, independent of who initiates contact.
- A patient and clinician should terminate their professional relationship before engaging in a sexual relationship.
- No clear recommendation exists as to when it is appropriate to initiate a sexual relationship *after termination of the professional relationship*.

COMPETENCE AND DECISION-MAKING CAPACITY

COMPETENCE

- A person's global and legal capacity to make decisions and to be held accountable in a court of law. All individuals are competent unless legally proven otherwise. Competence is assessed by the courts and is distinct from the term decision-making capacity.
- Incompetent patients, as assessed by the courts, or temporarily incapacitated patients may still be able to provide assent for treatment or refuse treatment. However, the need to treat supersedes the refusal of an incapacitated patient in emergency situations.

    - Example: A severely hypoxic patient with altered mental status who is unable to accept treatment may receive respiratory supportive therapy, as this constitutes a medical emergency.
- Incompetent patients can nonetheless have adequate decision-making capacity to refuse treatment. In these cases, autonomy supersedes beneficence.
    - Example: Patients living with a psychiatric illness, autism, or intellectual disabilities may be deemed incompetent in managing their finances, while maintaining adequate capacity to refuse treatment.

DECISION-MAKING CAPACITY

The ability of a patient to understand relevant information, appreciate the severity of the medical situation and its consequences, communicate clear and consistent choices, and deliberate rationally about their values in relation to the decision being made. This can be assessed by any clinician, based on a neurologic examination evaluating memory, comprehension, reasoning, and judgment.

- Testing for decision-making capacity does not always require a psychiatric consultation. It can be assessed by any clinician.
- Decision-making capacity is best understood as varying with the complexity of the decision involved.
    - Example: The level of capacity needed for a decision about liver transplantation is different from that needed to choose between two types of pain medication for fracture-related pain.
- In general, patients who have decision-making capacity have the right to refuse or discontinue treatment.
    - Example: A patient living with cancer with decision-making capacity can opt out of oncologic treatment.
- A patient's decision to refuse treatment can be overruled if the choice endangers the health and welfare of others.
    - Example: A patient with active tuberculosis (TB) must undergo antibiotic treatment because not treating the patient would pose a public health threat.
- All suicidal patients are considered to lack capacity.
- Occasionally, psychiatric evaluation can be recommended when decision-making capacity is equivocal. In cases where capacity is clearly impaired or intact, there is no need for psychiatric evaluation.

Q 1

A 47-year-old man is diagnosed with pancreatic cancer. His diagnosis and treatment options are discussed, but the patient does not want any intervention. He states that he would like to go home to his spouse and children to die peacefully. What is the most appropriate next step in management?

Q 2

A 51-year-old man is brought to the emergency department after he was struck by a motor vehicle while crossing the street. He is unresponsive and in need of emergent surgery. His spouse and children cannot be reached. What is the most appropriate next step in treatment?

INFORMED CONSENT

- Willing and voluntary acceptance of a specific medical intervention by a patient after adequate discussion with a clinician about the nature of the intervention along with its indications, risks, benefits, and potential alternatives (including no treatment).
- Informed consent should be obtained in the language the patient can clearly communicate and understand. If needed, an official translator should be used.
- Informed consent is given for a specific procedure, so that autonomy supersedes beneficence.
- Informed consent should be obtained by the doctor performing the procedure.
- Patients may change their minds at any time even after agreeing to the procedure. The healthcare team will honor the wishes of the patients and support the decision.
- Informed consent is required for significant procedures except for the following:
  - When emergency treatment is required. Example: An unconscious patient presents with cerebral edema after a motor vehicle collision, or a patient without previously indicated DNR/DNI (do not resuscitate/do not intubate) status undergoes cardiac arrest.
  - In the case a patient lost consciousness and no family member is around to provide consent for a procedure, a witnessed telephone consent is valid if that is the only way to obtain consent.
  - When a patient lacks decision-making capacity. In this case, consent is still required but must be obtained from a surrogate decision maker. Example: Minors generally require surrogate decision makers until they demonstrate adequate decision-making capacity or are of legal age.

KEY FACT

Patients with psychiatric illness can give consent if their decision-making capacity is intact.

Informed Consent for Incapacitated Individuals

MNEMONIC

BRAIN of informed consent—

Benefits
Risks
Alternatives
Indications
Nature

When individuals lose consciousness, doctors and caregivers should respect the patient’s last known wishes, whether expressed orally or in writing. Oral wishes, however, are more difficult to prove.

- Example: If a patient repeatedly did not want a procedure performed, performing the surgery cannot be performed once the patient loses consciousness.

Informed Consent in Reproductive Health

- The mother's autonomy supersedes the rights of the fetus.
- Except when acting as a surrogate decision maker for the pregnant patient, the father has no legal right to provide informed consent on a pregnancy-related procedure.
- Adults have access to sterilization. Consent is needed from the patient only and not the partner.

Informed Consent for a Never-Competent Person

In the case informed consent should be obtained for a never-competent person but no guardian is present, a court-designated third party should make a decision for the medical intervention based on the best interests of the patient.

Informed Consent for Minors

- In general, minors (people <18 years of age) cannot consent for their own medical treatment and require parents or guardians to consent on their behalf (one parent is sufficient as long as that parent has custody), except in the following situations:
    - **Life-threatening emergencies:** When parents cannot be contacted, parental consent is implied. A court order is not appropriate, as it delays the urgent intervention.
    - **Legal emancipation:** Emancipated minors do not require parental consent for medical care. Although emancipation laws vary from state to state, in general minors are emancipated if they are married, are in the armed services, are the parent of a child that they themselves support, or are financially independent of their parents and have obtained legal emancipation.
    - **Sexually transmitted infections and substance abuse treatment:** Rules concerning contraception, pregnancy, HIV, and treatment for drug and alcohol dependency vary across the United States.
- In cases discussed earlier, treating the patient without notifying the parents is acceptable.
- In cases where minors are seeking an abortion, encouraging patients to discuss with and notify parents/guardians is likely the best answer. There is no national standard as to whether clinicians should notify parents themselves.

1 A

The most appropriate next step in management is to respectfully ask the patient about his reasons for not wanting to pursue treatment. Patients often need clarification and reassurance. If he continues to decline treatment, abide by his decision (respect for autonomy).

2 A

The most appropriate next step is to proceed with the surgery. A clinician may give emergent treatment in the absence of informed consent when immediate intervention is necessary to prevent serious harm or death.

- In some states, the clinician is left with the decision of informing parents about adolescent use of confidential services in the interest of best serving the patient; other states limit disclosure.

Refusal of Treatment

- A parent has the right to refuse treatment for their child as long as those decisions do not pose a serious threat to the child's well-being.
- In nonemergent situations, the clinician in charge is responsible of engaging with the parents and care partners by providing education and clarification regarding the treatment.
  - When faced with continued resistance despite discussions with the parents, if the parental decision is not in the best interest of the child, the clinician should seek a court order (eg, refusing immunizations is not considered a serious threat; therefore the parent has the right to refuse).
- In an emergent situation, if a parental decision is not in the best interest of the child, a clinician may provide treatment against parental wishes. As such, if withholding treatment jeopardizes the child's safety, treatment can be initiated on the basis of legal precedent. In the case a child presents to the hospital with severe intra-abdominal hemorrhage and a blood transfusion appears to be necessary and lifesaving, the clinician can override the request of parents not to transfuse in order to save the life of the patient.
  - Example involving Jehovah's Witnesses: A clinician provides a blood transfusion to save the life of a 6-year-old child seriously injured in a motor vehicle collision despite parental requests to withhold such a measure.

KEY FACT

Brain death is the irreversible loss of all brain activity and is equivalent to cardiopulmonary death. If a patient is brain dead, no consent is needed to stop therapy. Two clinicians are required to perform a brain death examination to legally declare a patient brain dead.

END-OF-LIFE ISSUES

ADVANCE DIRECTIVES

An advance directive is a way for patients to let their doctors know what the patient's wishes are in case they lose capacity. A formal advance directive, such as a living will or healthcare proxy, will override the wishes of the family. Advance directives are legal documents that should be completed by any competent adult.

- **Living will:** A written advance directive outlining the patient's wishes. It addresses a patient's wishes to maintain, withhold, or withdraw life-sustaining treatment in the event of terminal disease or a persistent vegetative state when the patient has lost the capacity to make decisions. A living will can be a detailed document describing what tests and interventions the patient would refuse or consent to. If the living will is not detailed, decision making can be more difficult (eg, a living will stating no extraordinary care). This advance directive does not provide enough clarification and medical guidance for clinicians to follow. The definition of extraordinary care is subjective. It can mean no chemotherapy to some patients, but for others it could mean no invasive blood draws.

- **Physician orders for life-sustaining treatment:** POLST is a clinician's order that outlines a plan for end-of-life care that reflects both the patient's preferences concerning care at life's end and the clinician's judgment, based on a medical evaluation. The POLST is not a replacement of an advance directive.

Q

A 5-year-old girl with hydrocephalus needs another revision of her ventriculoperitoneal shunt. There are no satisfactory alternatives available to relieve her symptoms. Her father consents, but her mother does not want to proceed with the procedure, explaining that she has been through enough procedures in her young life. What is the most appropriate next step in management?

SURROGATE DECISION MAKING

When faced with an unconscious patient or a patient who cannot make a decision for themselves, surrogate decision making comes into play. The following scenarios are examples of such:

MNEMONIC

In the absence of a living will or durable power of attorney for healthcare—

The spouse CHIPS in For the patient

Adult **CHI**ldren
Parent
Sibling
Friend (in this order)

- **Durable power of attorney for healthcare or "healthcare proxy":** Legally designates a surrogate healthcare decision maker if a patient lacks decision-making capacity. More flexible than a living will. Surrogates should make decisions consistent with the person's stated wishes regarding medical care only. The healthcare proxy makes decisions based on the patient's verbal and written communicated wishes. The proxy's decision outweighs the family wishes.
- **No living will:** If no living will or durable power of attorney for healthcare exists, decisions should be made by close family members (spouse, adult children, parents, and adult siblings) or friends, in that order.
  - When all are in agreement, decision making on an intervention is straightforward.
  - When family members disagree, the clinician should first encourage discussion. If no consensus is agreed upon, refer the case to the hospital's ethics committee. Seek a court referral as a last resort.
- Ethics committees or court orders can be helpful when the patient lacks capacity, when the patient has no proxy or advance directive and there is disagreement among family members, or when there is disagreement between the family and healthcare team (eg, in cases of medical futility or parental refusal of necessary treatment for minors).

Do not resuscitate (DNR)/do not intubate (DNI) orders:

KEY FACT

Do not resuscitate (DNR) and do not intubate (DNI) orders do not mean “do not treat.”

- DNR and DNI orders are based on patient preferences regarding cardiopulmonary resuscitation (CPR) and intubation only. Patients can refuse all nonpalliative treatments or specific therapies (eg, CPR, intubation, antibiotics, feeding tubes).
- A DNR/DNI order does not prevent people from getting other interventions (eg, dialysis, chemotherapy, blood transfusions).

WITHDRAWAL OF LIFE-SUSTAINING TREATMENT

- Patients and their decision makers have the right to forego or withdraw life-sustaining treatment. Also, the clinician should never use the term withdrawal of care because healthcare staff do not stop caring for a patient. Clinicians should seek to understand patients and their reasons for refusing beneficial treatments.
- When a patient has full capacity and decides to withdraw life-sustaining treatment, there is no need for a psychiatric evaluation. Psychiatric evaluations are only needed if the patient’s capacity to understand is uncertain.
- No ethical distinction is made between withholding a treatment and withdrawing a treatment, because a patient may choose to refuse an intervention either before or after it is initiated. This can include ventilation, fluids, nutrition, and medications such as antibiotics.

A

The most appropriate next step in management is to proceed with the shunt revision. The consent of one parent is sufficient to proceed with the treatment of a minor, particularly when it is unequivocally clear that the decision is in the child’s best interest.

EUTHANASIA AND CLINICIAN-ASSISTED SUICIDE

- Euthanasia is the administration of a lethal agent by the healthcare provider with the intent to end life.
  - It is opposed by the American Medical Association (AMA) Code of Medical Ethics and is illegal in all states.
  - Patients who request euthanasia should be evaluated for inadequate pain control and comorbid depression.
- Clinician-assisted suicide consists of prescribing a lethal agent to a patient who will self-administer it to end his or her own life. This is currently illegal except in the states of Oregon, Washington, Vermont, Colorado, and California. This is also legal via court order in Montana.

HOSPICE CARE

- Hospice care is a subtype of palliative care focused on palliation of symptoms for patients with a poor prognosis. The focus is on pain management, quality of life, and bereavement.

- If the intent is to relieve suffering and if the medications administered are titrated for that purpose, it is considered ethical to provide palliative treatment to relieve pain and suffering even if it may hasten a patient’s death (principle of double effect).

FUTILE TREATMENT

Clinicians are not ethically obligated to provide treatment and may refuse a patient’s or family member’s request for further intervention on the grounds of futility under any of the following circumstances:

- There is no evidence or pathophysiologic rationale for the treatment.
- The intervention has already failed.
- Maximal intervention is currently failing.
- Treatment will not achieve the goals of care.

COMPLEMENTARY AND ALTERNATIVE MEDICINE THERAPY

Complementary and alternative medicine (CAM) represents medical services and practices that are not part of standard medical care. As the name indicates, this can include special diets, vitamins, dietary/herbal supplements, meditation, yoga, and hypnosis, among others. These alternative treatments help patients cope with their disease and side effects of their disease such as nausea, fatigue, pain, and loss of appetite. If a patient is interested in alternative/nontraditional treatment, the clinician should obtain more information as to why the patient is interested. The clinician should provide as much information as possible, and they should not dismiss the patient.

DISCLOSURE

FULL DISCLOSURE

- Disclosure is the act of making something known in its entirety. Medically, patients have a right to know about their medical status, prognosis, and treatment options (full disclosure). They have the legal right to obtain copies of their medical records within a specified timeframe.
- Per the right to autonomy, a patient’s family cannot require that a clinician withhold information from the patient without the knowledge and consent of the patient. When such a case arises, the clinician should explore why the family member does not want the diagnosis revealed. Ultimately, however, the patient should be told.
- A clinician may withhold information only if the patient requests not to be told or in the rare and controversial case in which a clinician determines that disclosure would cause severe and immediate harm to the patient (therapeutic privilege). This may include any information that may lead to depression, anxiety, or even resignation from a current job.
- Therapeutic privilege does not involve withholding medical information in emergency situations or reporting errors in patient care.
- Disclosure is to be done at the earliest time possible, and it is withheld only if there are contraindications to communicating this information to the patient (ie, if it might do more

harm to the patient than good).

- If issues arise when information is being disclosed, this is handled by discussing with the patient's family as to why they don't want disclosure without actually letting them know the details of the information being disclosed. Alternatively, this can be discussed with the ethics committee if there appears to be a conflict of interest (eg, debate between two siblings over what their parent would have wanted).

SETTING FOR DELIVERING NEWS

News, good or bad, needs to be disclosed to the patient in a way that it is fully understood, without breach of privacy, and with empathy. A setup needs to be created whenever delivering news so that all these concerns, and more, can be addressed directly.

The most commonly followed model is the SPIKES model. This includes the following:

- **S**etup: This requires the area of news delivery to be in a private area, ideally with everyone sitting down for the discussion. It is also important to include people who the patient thinks should hear the news (with consent by the patient first).
- **P**erception of the patient: The next step entails asking the patient what they know so far about their illness. It is important to know what they think that the news might be: good or bad?
- **I**nvitation from the patient: Also, it is important to ask them what information they would like to hear and what they feel like they want to exclude. If the patient thinks they do not want to include certain pieces of information in the discussion, they should be asked why. However, it is important to remember that as much as the patient has the right to know, the patient also has the right not to know.

After this, the clinician should initiate discussion of the news in stages.

- **K**nowledge: This stage is when all the information about the patient's current condition is delivered. It is important to know the intellectual level of the patient to make sure that the patient understands what information is being communicated to them. Special circumstances may require detailed diagrams that are simplified for the patient.
    - Always give information bit by bit, and make sure that you consider the patient's current emotional state prior to giving information.
    - Always be gentle and caring. Examples include statements like: "I am sorry to let you know...", or "I think this piece of information may be particularly disturbing for you..."
- **E**motions: Prepare to identify any emotion that the patient shows, acknowledge it, and respond in an empathetic manner. Examples include statements such as "I know this might be difficult to hear..." or "I know this might not be what you had anticipated..."
- **S**trategy and summary: Let the patient know that the information you needed to deliver, and that the patient wanted to hear, has now been communicated. Ask the patient if they have any queries or if they have anything else that they might want to hear. If not, ask them about when they may be ready for the next meeting and briefly outline what will be discussed next. Examples include statements like: "Although this news might have come unexpectedly for you, we still need to discuss your care plan. While you process this information, we also need to discuss how to proceed further with your care. If you want to discuss this further, then we can continue. Otherwise, please let me know when you would like to discuss this next."

CONFIDENTIALITY

- Patient security, privacy, and healthcare data protection fall within the auspices of the Health Insurance Portability and Accountability Act (HIPAA). This law addresses three main issues: privacy (for use and disclosure of individuals' health information), security (to set national standards for protecting confidentiality, integrity, and availability of electronically protected healthcare-related information), and breach rules (to notify affected individuals, federal government, and media about unsecured protected health information).

MNEMONIC

Overriding confidentiality—

WAITT a SEC before letting a patient in danger go!

WOUNDS
Automobile-driving impairment
Infectious disease
Tarasoff (violent crimes) and human **T**rafficking
Suicide
Elder abuse and neglect
Child abuse

- Protected health information is any information that is transmitted or maintained in electronic media directly related to an individual's healthcare. This may also involve any verbal communications (eg, talk over coffee or lunch) that discloses patients' identifiable health information (eg, name, patient number). This can also include bills, admission profile, prescription records, referral, discharge, and follow-up appointments.
- Information disclosed by a patient to their clinician and information about a patient's medical condition are strictly confidential and should be discussed and accessed only by those directly involved in the patient's care, with few exceptions (described later). This may require disclosure to a healthcare monitoring body like the Centers for Disease Control or Prevention (CDC), or even to the police.
- Who has access to medical records? This is typically reserved only for the patient or their authorized representatives. A patient may waive the obligation of the clinician to protect confidentiality (eg, with insurance companies, authorized family members), preferably by way of written or verbal consent. The clinician should disclose only the minimally necessary information to these personnel.

It is ethically and legally necessary to override confidentiality in the following situations:

- **Patient intent to commit a crime against an identifiable victim (*Tarasoff* decision):** Clinicians have a duty to protect the intended victim through reasonable means (eg, warn the victim, notify police).

KEY FACT

Signs of suspected child abuse:

History given not consistent with injury
Unusual child or parental behavior
Delay in seeking medical care
Subdural hematomas
Retinal hemorrhages
Spiral, bucket-handle, or rib fractures
Injuries in different stages of healing

- **Suicidal patients.**
- **Child abuse/neglect and elder abuse/neglect.**
- **Reportable infectious diseases** (eg, HIV, sexually transmitted infections, TB, polio, diphtheria, rabies, enteric fever, tetanus, COVID-19): There is a duty to warn public officials and identifiable people at risk. It is normally best to encourage patients themselves to inform sexual contacts who are at risk for contracting the illness.
- **Reportable noninfectious diseases:** These include cancer, carbon monoxide poisoning, silicosis, and lead poisoning.

KEY FACT

Potential signs of elder abuse and neglect:
Cuts, bruises, pressure ulcers, burns
Uncommon fractures
Malnutrition or dehydration
Anogenital injury or infection
Evidence of poor caretaking or financial exploitation

- **Notifiable outbreaks:** These include food- and water-borne disease outbreaks. Currently patients affected by the COVID-19 pandemic are also reportable.
- **Gunshot and knife wound** (a duty to notify the police): Such instances also include emergency scenarios when the treating clinician is trying to obtain consent over the phone because the patient cannot provide one.
- **The patient is a danger to others** (eg, impaired automobile drivers): Currently, only six states have mandatory clinician reporting laws.
  - Example: A patient begins to drive 1 week after hospitalization for seizures, although the department of motor vehicles in his state requires that licensed drivers be without seizures for at least 3 months.

KEY FACT

Guiding principles for overriding confidentiality:
There is an identifiable third party at risk for harm.
The harm is significant and probable.
Disclosure will help prevent or mitigate the harm.
Other measures, such as convincing the patient to self-disclose, have failed.

CLINICAL RESEARCH

The formal definition of clinical research is any medical research that tests new investigations, treatments, and therapies on people or against a standard of care.

- The role of ethics in research is to ensure patient safety and integrity of research results. The Declaration of Geneva of the World Medical Association (WMA) binds the clinician with the statement: "The health of my patient will be my first consideration," which implies that the patient should be protected from harmful treatment at all times. As such, patients may choose voluntarily to be research subjects, or they may be enrolled in a therapeutic trial for a disease without any known cure to see if they may benefit from the treatment.
- The Declaration of Helsinki addresses ethical concerns that arise from such studies. It also mentions that clinicians are obligated to inform patients considering involvement in a clinical research protocol about the purpose of the research study and the entire study design as it will affect the patient's treatment. This includes the possible risks, benefits, and alternatives to the research protocol. Clinicians are also obligated to inform the participants that no patient identification label (eg, name, patient number) will be used in the research.

CORE PRINCIPLES OF CLINICAL RESEARCH

The principles followed include the following:

- Ensuring compliance with clinical protocols, with repeated reviews confirming the same during the time of research
- Verification of scientific validity of results
- Ensuring a fair system of selecting treatment options, with removal of bias where possible
- Obtaining informed consent discussing benefit and harm prior to participation in research

KEY FACT

Mandatory reporting of intimate partner violence is controversial and varies by state. Nonetheless, clinicians should document the encounter, offer support, and have resources available for assistance.

ETHICAL CONCERNS

- Pregnant patients: Ensure no harm comes to both mother and child during research.
- Children: It is important to obtain assent of the child, even though the consent from the guardians is mandatory.
- Incurable illness: The clinician should make sure the patient does not enroll only for anticipated personal benefit.
- Monetary compensation: Such compensation may provide undue influence for accepting the risk for contracting a disease or being harmed in the process. Most trials provide only out-of-pocket expenses as compensation.
- Recruitment: The patient may be enrolled in multiple trials due to lack of volunteers or due to rarity of disease. This may lead to bias in the results and to patient harm.

- Stem cell research: Such research has an intrinsic difficulty with maintaining anonymity of human tissue donors, ownership of tissue, long-term storage of samples, and manipulation of genetic material to create new organisms.
- Inability for patient to consent: In this case, the clinician should obtain consent from the legally authorized representative.
- Incarcerated patients: Incarceration does not change the process of consent or healthcare rights.

CONFLICT OF INTEREST

- Occurs when clinicians find themselves having a personal interest in a given situation, which influences their professional obligations.
    - Example: A clinician may own stock in a pharmaceutical company (financial interest) that produces a drug he is prescribing to his patient (patient care interest).
- Clinicians should disclose existing conflicts of interest to affected parties (eg, patients, institutions, audiences of journal articles or scientific meetings).
    - Accepting gifts from pharmaceutical companies can influence a clinician’s practice and should generally be avoided. Nonmonetary gifts should be accepted only if they will directly benefit patient care and are of small monetary value. A clinician should never accept cash.

GIFTS FROM PATIENTS

- A patient or patient party may offer to provide the treating healthcare team or a particular member in the team with a gift as an expression of gratitude or as a reflection of the patient’s culture.
- Accepting gifts or cash to influence care or preferential treatment is unacceptable. This can further harm the patient-doctor relationship.
- When accepting a gift, keep the following in mind:
    - Do not allow the gift or offer to influence care.
    - Decline gifts if acceptance may present financial or emotional hardship to the gifting family.
    - Be sensitive about the patient’s emotions and be fair (accepting a gift may lead to impaired relationship among team members if the gift is provided disproportionately).

Q

A 35-year-old woman visits a primary care clinician after hurting her wrist. Physical exam reveals circumferential bruises of her wrist, neck, and arms. The patient admits that the injuries were inflicted by her partner. What is the most appropriate next step in management?

GIFTS FROM DRUG COMPANIES

- Governed by the Sunshine Act, which requires clinicians to disclose any financial information or conflict of interest required by employers, advisory board, and institutions that provide research funding.

- Includes gifts that cost more than $10 or any small gifts that are worth cumulatively a sum of more than $100.
- Exemptions include certified and accredited continuing medical education, buffet lunch and snacks at large-scale events, product samples not intended for sale, education material for patients, charitable items, or loaned devices for a trial period of less than 90 days.
- However, such gifts, or any advertisements, if received, should not alter the appropriate evidence-based practice of medicine on the clinician's part.

MALPRACTICE

DEFINING MALPRACTICE

Medical malpractice occurs when a hospital, doctor, or other healthcare professional causes injury or permanent harm to a patient as a result of a negligent act of carelessness. This may occur in two different ways: acts of omission (breach of duty to provide appropriate care to patients when capacity to consent was not determined) or acts of commission (doing something purposefully that leads to harm, despite being aware of possible outcomes without notifying the patient of such outcomes).

The essential elements of a civil suit under negligence include:

- The clinician has a **D**uty to the patient.
- **D**ereliction of duty occurs.
- There is **D**amage to the patient.
- Dereliction is the **D**irect cause of damage.

An exception involves the "Good Samaritan" laws, which protect those who have completed basic first aid training and are certified by a healthcare organization. These laws apply mostly to those people who may respond to victims in good faith and in a rational manner, with the aim of preventing harm.

Unlike a criminal suit, in which the burden of proof is "beyond a reasonable doubt," the burden of proof in a malpractice suit is "a preponderance of the evidence."

Clinicians may refuse inappropriate requests, such as demanding to be seen after hours. The clinician should set clear limits and professional boundaries while remaining calm. If the patient has a nonurgent condition, the clinician should not recommend that the patient visit the emergency department.

MNEMONIC

The 4 Ds of malpractice—

Duty
Dereliction
Damage
Direct cause

IMPAIRED PRACTICING CLINICIAN

Impairment does not only refer to aging. Per the AMA, an impaired clinician is one whose physical or mental health interferes with their ability to safely engage in professional activities. This can also involve anxiety (a major stress factor that affects job performance and working memory), burnout (emotional exhaustion, depersonalization, reduced sense of personal accomplishment), and those clinicians with substance use disorder.

A clinician has an obligation to protect patient interests and ensure appropriate care and assistance to other clinicians/colleagues who may be impaired physically or mentally. They should also report impaired colleagues to the peer review body of the hospital (eg, the program director or medical director) or the local or state medical board when the physician does not have hospital privileges. When compromise of a patient's health and safety is an immediate threat, report directly to the state licensing board. If the situation does not change despite prior reporting, report to a higher authority.

- Example: A clinician notes that his colleague, a surgeon, gets repeatedly drunk at parties throughout the week and comes late to work the next day. A patient has recently filed a malpractice lawsuit, as the patient believes that the doctor operated on him in a drunken state. Your responsibility in this case is to refer the clinician to a clinician health program for further evaluation and possible therapy.

A

The most appropriate next step would be to offer support and acknowledge the courage it takes to discuss abuse. Assess the safety of the woman and of any children involved, introduce the concept of an emergency plan, and encourage the use of community resources. If the patient consents, report the abuse to relevant authorities.

HIGH-YIELD FACTS IN

GASTROINTESTINAL

- Oral and Salivary Gland Disease
  - ORAL LESIONS
  - OROPHARYANGEAL CANCERS
  - SALIVARY GLAND DISEASE
- Esophageal Disease
  - DYSPHAGIA/ODYNOPHAGIA
  - INFECTIOUS ESOPHAGITIS
  - PILL (MEDICATION-INDUCED) ESOPHAGITIS
  - EOSINOPHILIC ESOPHAGITIS
  - ESOPHAGEAL RINGS
  - PLUMMER-VINSON SYNDROME
  - DISTAL ESOPHAGEAL SPASM
  - ACHALASIA
  - ESOPHAGEAL DIVERTICULA
  - GASTROESOPHAGEAL REFLUX DISEASE
  - HIATAL HERNIA
  - ESOPHAGEAL CANCER
- Gastrointestinal Bleeding
  - UPPER GI BLEEDING
- Disorders of the Stomach and Duodenum
  - DYSPEPSIA
  - GASTRITIS
  - GASTRIC CANCER
  - PEPTIC ULCER DISEASE
  - ZOLLINGER-ELLISON SYNDROME
  - GASTROPARESIS
  - MÉNÉTRIER DISEASE
  - GASTRIC BEZOAR
  - BARIATRIC SURGERY
- Disorders of the Small Bowel
  - DIARRHEA
  - MALABSORPTION/MALDIGESTION
  - CARBOHYDRATE MALDIGESTION
  - CARCINOID SYNDROME
  - SMALL BOWEL OBSTRUCTION
  - ILEUS
  - ACUTE ABDOMEN
  - DUODENAL HEMATOMA
  - MESENTERIC ISCHEMIA
  - ACUTE APPENDICITIS

Disorders of the Large Bowel
- CLOSTRIDIUM DIFFICILE COLITIS
- DIVERTICULAR DISEASE
- LARGE BOWEL OBSTRUCTION
- IRRITABLE BOWEL SYNDROME
- COLORECTAL CANCER
- COLORECTAL CANCER-ASSOCIATED CONDITIONS
- ISCHEMIC COLITIS
- MICROSCOPIC COLITIS

Anorectal Disease
- HEMORRHOID GRADING

Inflammatory Bowel Disease

Hernias

Biliary Disease
- CHOLELITHIASIS AND BILIARY COLIC
- CHOLECYSTITIS
- CHOLEDOCHOLITHIASIS
- CHOLANGITIS
- GALLSTONE ILEUS
- POSTCHOLECYSTECTOMY SYNDROME
- BILIARY CYST
- CHOLANGIOCARCINOMA

Liver Disease
- ABNORMAL LIVER ASSOCIATED ENZYMES
- HEPATITIS
- CIRRHOSIS
- SPONTANEOUS BACTERIAL PERITONITIS
- ISCHEMIC HEPATITIS
- ACUTE LIVER FAILURE
- HEPATORENAL SYNDROME
- HEPATOPULMONARY SYNDROME
- HEPATIC HYDROTHORAX
- TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT PROCEDURE
- PRIMARY SCLEROSING CHOLANGITIS
- PRIMARY BILIARY CHOLANGITIS
- NONALCOHOLIC FATTY LIVER DISEASE
- HEPATOCELLULAR CARCINOMA
- HEMOCHROMATOSIS
- WILSON DISEASE (HEPATOLENTICULAR DEGENERATION)
- LIVER TRANSPLANTATION
- BENIGN LIVER LESIONS

Pancreatic Disease
- PANCREATITIS

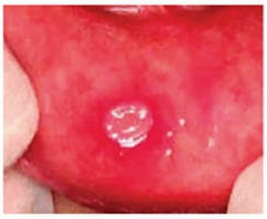
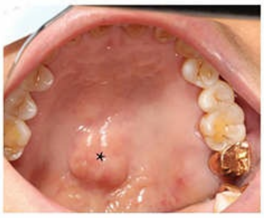
PANCREATIC CYSTS
PANCREATIC NONENDOCRINE TUMORS (PNETS)
PANCREATIC CANCER

ORAL AND SALIVARY GLAND DISEASE

ORAL LESIONS

Table 2.6-1 describes common benign oral lesions. Figure 2.6-1 depicts premalignant oral lesions. Although these lesions are noncancerous, they can transform into squamous cell carcinoma (SCC).

TABLE 2.6-1. Selected Benign Oral Lesions

CONDITION AND ETIOLOGY	PRESENTATION	DIAGNOSIS AND TREATMENT
Recurrent aphthous stomatitis 	Recurrent aphthous stomatitis is the most common cause of ulcerations in the mouth Ulcers are painful, shallow, and round/oval with a central yellow exudate Condition begins in childhood or adolescence, often resolving later in life Differential includes underlying causes of recurrent ulceration due to systemic conditions (eg, inflammatory bowel disease [IBD], celiac disease, systemic lupus erythematosus [SLE])	Administering topical corticosteroids and systemic immunomodulators Treating underlying systemic conditions Avoiding mucosal trauma, correcting vitamin deficiencies, or excluding obvious dietary causes can help
Torus palatinus 	Torus palatinus is a benign and asymptomatic midline bony overgrowth of the hard palate Imaging and biopsy are required for fast-growing mass, atypical appearance, or if the overgrowth is not in the midline Prevalence is up to 27% of the population	Generally, no treatment is required; surgical excision can be considered if the lesion is causing significant discomfort

(Image 1 adapted with permission from Peterson DE, O'Shaughnessy JA, Rugo HS, et al. Oral mucosal injury caused by mammalian target of rapamycin inhibitors: Emerging perspectives on pathobiology and impact on clinical practice. *Cancer Med.* 2016;5[8]:1897-1907. Image 2 adapted with permission from Chao PJ, Yang HY, Huang WH, et al. Oral tori in chronic hemodialysis patients. *Bio-med Res Int.* 2015;2015:897674.)

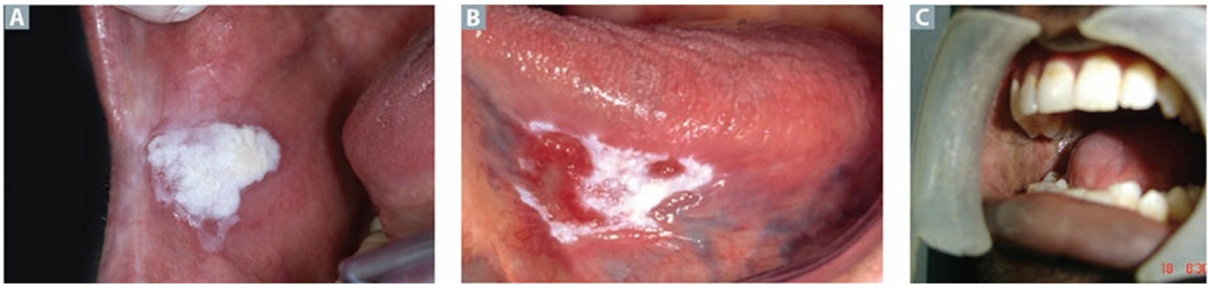


FIGURE 2.6-1. **Premalignant lesions of the mouth. (A)** Leukoplakia. **(B)** Erythroplakia. **(C)** Oral submucosal fibrosis. (Images A and B reproduced with permission from van der Waal I. Oral leukoplakia, the ongoing discussion on definition and terminology. *Med Oral Patol Oral Cir Bucal*. 2015;20[6]:e685-e692. Image C reproduced with permission from Saravanan K, Narayanan V. The use of buccal fat pad in the treatment of oral submucous fibrosis: A newer method. *Int J Dent*. 2012;2012:935135.)

Oral Leukoplakia

Generally asymptomatic, premalignant lesions that occur in 1.5% to 4.3% of the normal population.

KEY FACT

Oral hairy leukoplakia is a manifestation of EBV seen in immunocompromised patients. It affects the lateral portion of the tongue and presents with painless plaques that have a feathery or hairy appearance and **cannot be scraped off.** There is no malignancy potential.

History/PE

Patients present with white patches in the oral mucosa that cannot be scraped off (Fig. 2.6-1A). The reported rates of transformation to SCC vary widely, ranging from <1% to 36%.

Risk Factors

- Tobacco use, alcohol use, and human papilloma virus (HPV) infection.
- Risk factors for transformation to SCC: Nonhomogeneous lesions, large lesions (>4 cm diameter), multiple anatomic sites, high-risk location (lateral tongue and floor of the mouth), and dysplasia on histologic examination.

Diagnosis

- Definitive diagnosis is based on biopsy and histopathology.
- Histopathology may show hyperkeratosis, atrophy, inflammation, hyperplasia, or dysplasia. Occasionally there may be carcinoma in situ or invasive carcinoma.

KEY FACT

Oral candidiasis is an opportunistic, intraoral infection that most commonly presents with confluent white patches and plaques in the oral mucosa. They are differentiated from leukoplakia because they **can be scraped or wiped off,** exposing an erythematous base (see the Candidiasis section in the Dermatology chapter).

Treatment

- Options include surgical excision of smaller high-risk lesions. For larger lesions, risk factor modification (eg, cessation of smoking and alcohol use) and close clinical and histologic surveillance are indicated.
- Other options include destruction (with laser ablation or cryosurgery) and medical treatment (eg, retinoids, vitamin A).
- Lifelong follow-up is required due to high recurrence and development of squamous cell carcinoma.

Erythroplakia

Red, well-demarcated lesions commonly located on the floor of the mouth, the ventral tongue, or soft palate that cannot be explained by another disease (Fig. 2.6-1B). An estimated 2.7% of cases annually transform to SCC.

- ***Hx/PE:*** Generally asymptomatic in patients
- ***Risk factors:*** Most often found in older adults who use tobacco and consume alcohol
- ***Dx:*** Definitive diagnosis based on biopsy and histopathology, which may show dysplasia,

carcinoma in situ, or even invasive SCC
- ***Tx:*** Similar to leukoplakia

Oral Submucosal Fibrosis

Submucosal fibrosis of the whole oral mucosa (Fig. 2.6-1C). The estimated annual rate of transformation to SCC is 2% to 8%.

- ***Hx/PE:*** Burning, ulceration, and pain of the oral mucosa
- ***Risk factors:*** Chewing araca nuts (including betel quid, paan)
- ***Dx:*** Based on history and biopsy findings
- ***Tx:*** Discontinuing betel products—mainstay of treatment

Oral Lichen Planus

Inflammatory lesions of the skin and oral mucosa with a prevalence of 1% to 3% (see the Miscellaneous Skin Disorders section in the Dermatology chapter for more details). Oral lesions appear as reticular white plaques, mucosal erythema, or erosions most commonly affecting the buccal mucosa. The overall transformation rate to SCC is 1% to 2%.

- ***Hx/PE:*** Reticular white plaques that are rarely symptomatic. Other lesions can present with pain.
- ***Dx:*** Based on clinical evaluation and biopsy findings
- ***Tx:*** No treatment for asymptomatic disease. Treatment of symptomatic disease is with topical corticosteroids (first line). If ineffective, topical tacrolimus or pimecrolimus can be used. Refractory disease may require oral glucocorticoids or systemic immunomodulators.

OROPHARYNGEAL CANCERS

Oropharyngeal SCC is the most common oral cancer (up to 90% of all oral neoplasms). It most commonly arises from premalignant lesions such as leukoplakia, erythroplakia, or lichen planus.

History/PE

Patients may be initially asymptomatic. Most commonly, oral cancer presents as an ulcerated lesion with a central necrotic area with rolled-up borders. The most common locations are the lateral and ventrolateral parts of the tongue, although other areas may also be affected.

Risk Factors

- Smoking or use of smokeless tobacco
- Alcohol consumption
- Areca (betel) nut ingestion (more prevalent in developing countries)
- Sometimes associated with HPV-16 and chronic irritants (eg, certain mouthwashes)

Diagnosis

Diagnosis is based on biopsy and histopathology. Laryngoscopy, bronchoscopy, and esophagoscopy are required to rule out simultaneous second primary cancers. After diagnosis, head and neck CT and a x-ray of the chest (CXR) or positron emission tomography (PET)/CT are done to determine extent of spread and metastasis.

Treatment

Treatment is initially surgical resection. Lymph node dissections are done with significant nodal disease or deep invasion. Surgical reconstruction is important to reduce postsurgical disability. Postoperative chemotherapy or radiotherapy is used with high-risk or advanced disease. In many patients for whom surgical resection is challenging or overly morbid (or in certain subtypes [eg, HPV-associated cancers]), chemotherapy and radiation will be used as the definitive treatment with curative intent, with no surgery except in cases of relapse.

MNEMONIC

The RULE acronym helps physicians decide which oral lesions to biopsy.

Red/red-white lesions
Ulcers
Lumps
Especially in combination or if indurated

SALIVARY GLAND DISEASE

The sublingual, submandibular, and parotid glands are the most prominent salivary glands. Clinically, salivary gland swelling may be approached by identification of chronicity (acute vs chronic) and distribution (unifocal [single gland] vs multifocal [multiple glands]) of swelling. Figure 2.6-2 shows an outline of salivary gland pathologies based on this approach. Tables 2.6-2 and 2.6-3 describe selected non-neoplastic and neoplastic conditions in detail.

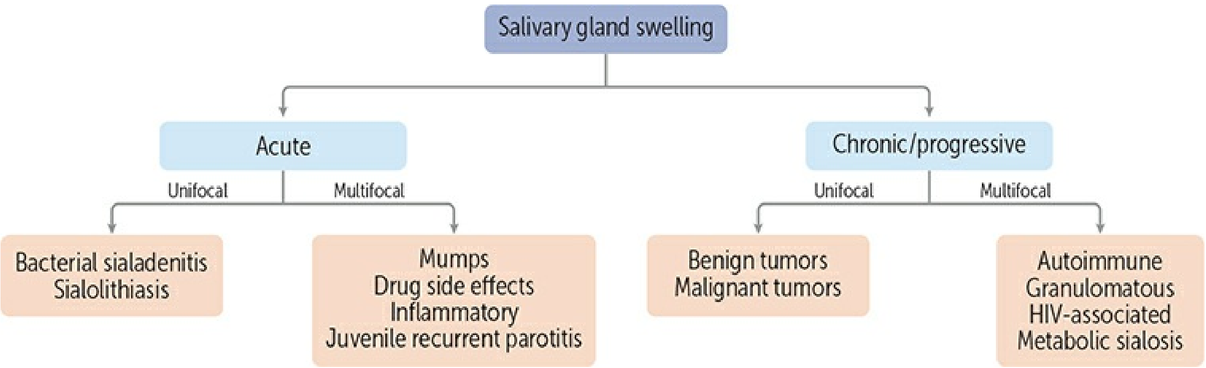
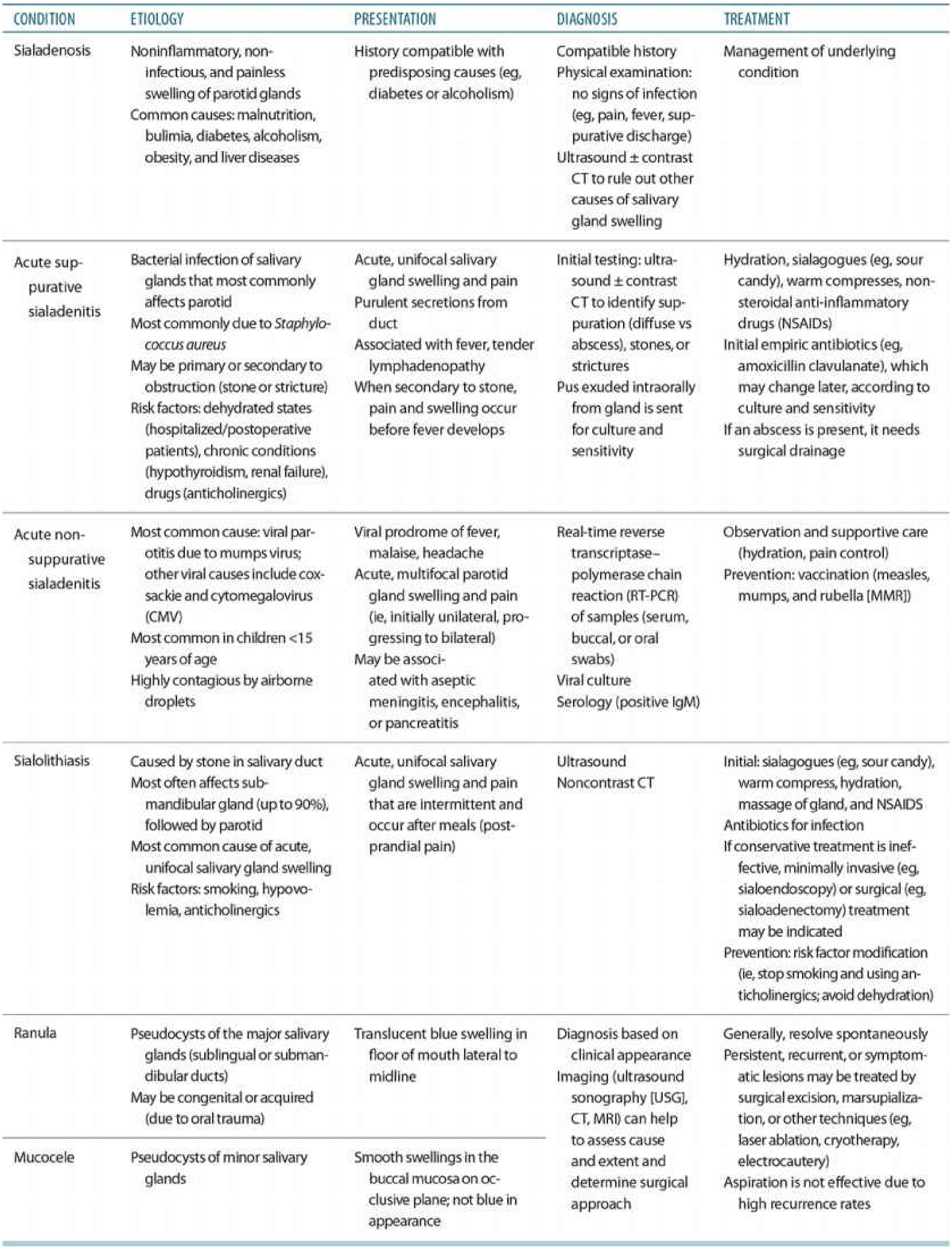

Salivary gland swelling
Acute
Chronic/progressive
Unifocal
Multifocal
Unifocal
Multifocal
Bacterial sialadenitis
Sialolithiasis
Mumps
Drug side effects
Inflammatory
Juvenile recurrent parotitis
Benign tumors
Malignant tumors
Autoimmune
Granulomatous
HIV-associated
Metabolic sialosis

FIGURE 2.6-2. **Causes of salivary gland swelling.** (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.6-2. **Selected Non-neoplastic Causes of Salivary Gland Swelling**



CONDITION	ETIOLOGY	PRESENTATION	DIAGNOSIS	TREATMENT
Sialadenosis	Noninflammatory, noninfectious, and painless swelling of parotid glands Common causes: malnutrition, bulimia, diabetes, alcoholism, obesity, and liver diseases	History compatible with predisposing causes (eg, diabetes or alcoholism)	Compatible history Physical examination: no signs of infection (eg, pain, fever, suppurative discharge) Ultrasound ± contrast CT to rule out other causes of salivary gland swelling	Management of underlying condition
Acute suppurative sialadenitis	Bacterial infection of salivary glands that most commonly affects parotid Most commonly due to *Staphylococcus aureus* May be primary or secondary to obstruction (stone or stricture) Risk factors: dehydrated states (hospitalized/postoperative patients), chronic conditions (hypothyroidism, renal failure), drugs (anticholinergics)	Acute, unifocal salivary gland swelling and pain Purulent secretions from duct Associated with fever, tender lymphadenopathy When secondary to stone, pain and swelling occur before fever develops	Initial testing: ultrasound ± contrast CT to identify suppuration (diffuse vs abscess), stones, or strictures Pus exuded intraorally from gland is sent for culture and sensitivity	Hydration, sialagogues (eg, sour candy), warm compresses, nonsteroidal anti-inflammatory drugs (NSAIDs) Initial empiric antibiotics (eg, amoxicillin clavulanate), which may change later, according to culture and sensitivity If an abscess is present, it needs surgical drainage
Acute nonsuppurative sialadenitis	Most common cause: viral parotitis due to mumps virus; other viral causes include coxsackie and cytomegalovirus (CMV) Most common in children <15 years of age Highly contagious by airborne droplets	Viral prodrome of fever, malaise, headache Acute, multifocal parotid gland swelling and pain (ie, initially unilateral, progressing to bilateral) May be associated with aseptic meningitis, encephalitis, or pancreatitis	Real-time reverse transcriptase–polymerase chain reaction (RT-PCR) of samples (serum, buccal, or oral swabs) Viral culture Serology (positive IgM)	Observation and supportive care (hydration, pain control) Prevention: vaccination (measles, mumps, and rubella [MMR])
Sialolithiasis	Caused by stone in salivary duct Most often affects submandibular gland (up to 90%), followed by parotid Most common cause of acute, unifocal salivary gland swelling Risk factors: smoking, hypovolemia, anticholinergics	Acute, unifocal salivary gland swelling and pain that are intermittent and occur after meals (postprandial pain)	Ultrasound Noncontrast CT	Initial: sialagogues (eg, sour candy), warm compress, hydration, massage of gland, and NSAIDS Antibiotics for infection If conservative treatment is ineffective, minimally invasive (eg, sialoendoscopy) or surgical (eg, sialoadenectomy) treatment may be indicated Prevention: risk factor modification (ie, stop smoking and using anticholinergics; avoid dehydration)
Ranula	Pseudocysts of the major salivary glands (sublingual or submandibular ducts) May be congenital or acquired (due to oral trauma)	Translucent blue swelling in floor of mouth lateral to midline	Diagnosis based on clinical appearance Imaging (ultrasound sonography [USG], CT, MRI) can help to assess cause and extent and determine surgical approach	Generally, resolve spontaneously Persistent, recurrent, or symptomatic lesions may be treated by surgical excision, marsupialization, or other techniques (eg, laser ablation, cryotherapy, electrocautery) Aspiration is not effective due to high recurrence rates
Mucocele	Pseudocysts of minor salivary glands	Smooth swellings in the buccal mucosa on occlusive plane; not blue in appearance		

TABLE 2.6-3. **Selected Benign and Malignant Tumors of Salivary Glands**

CONDITION	ETIOLOGY	PRESENTATION	DIAGNOSIS	TREATMENT
Pleomorphic adenomas (benign)	Most common salivary gland tumor in adults Majority in parotid gland, followed by submandibular May undergo malignant transformation and recurrence Associated with ionizing radiation exposure, viral infection, smoking, and exposure to chemicals (eg, rubber manufacturers, cosmetics)	Chronic, unifocal, painless, slow-growing mass or swelling in malignant and benign disease Signs of malignancy: pain, facial paresis, fixed mass, and cervical lymphadenopathy	Ultrasonography, CT, MRI, and sometimes PET-CT Fine-needle aspiration biopsy or ultrasound-guided core needle biopsy can confirm diagnosis	Surgical excision—mainstay of treatment no matter if benign or malignant Postoperative radiation therapy in select cases Cervical lymph node dissection may be required in malignant disease or with presence of other high-risk features (eg, high-grade tumors, facial nerve weakness) Important risks of surgery: facial nerve dysfunction and Frey syndrome (sweating when chewing)
Mucoepidermoid carcinoma (malignant)	Most common malignant salivary gland neoplasm Commonly in parotid Low-grade with good prognosis if treated early	Painless, slow-growing mass that is firm or hard	Based on histologic examination	Surgical excision recommended for localized resectable disease Postoperative or palliative radiotherapy may be used
Adenoid cystic carcinoma (ACC; malignant)	Second most common malignant salivary gland neoplasm Most common in submandibular gland Invades facial nerve early, thus facial weakness or paralysis Local recurrence after excision	Most commonly arises in the salivary glands or other areas within the head and neck region; symptoms of ACC of the salivary glands may include numbness of the lower lip and/or other facial areas, nerve impairment causing weakness of certain facial muscles, ongoing pain, and/or other associated abnormalities	Based on histologic examination	Standard therapy includes surgical removal of the malignancy and affected tissue followed by radiation; if initial surgery is not an option due to the specific location and/or progression of the malignancy, therapy may include radiation alone

ESOPHAGEAL DISEASE

DYSPHAGIA/ODYNOPHAGIA

Difficulty swallowing (dysphagia) or pain with swallowing (odynophagia) caused by abnormalities of the oropharynx or esophagus. Figure 2.6-3 illustrates approaches to the diagnosis of esophageal dysphagia.

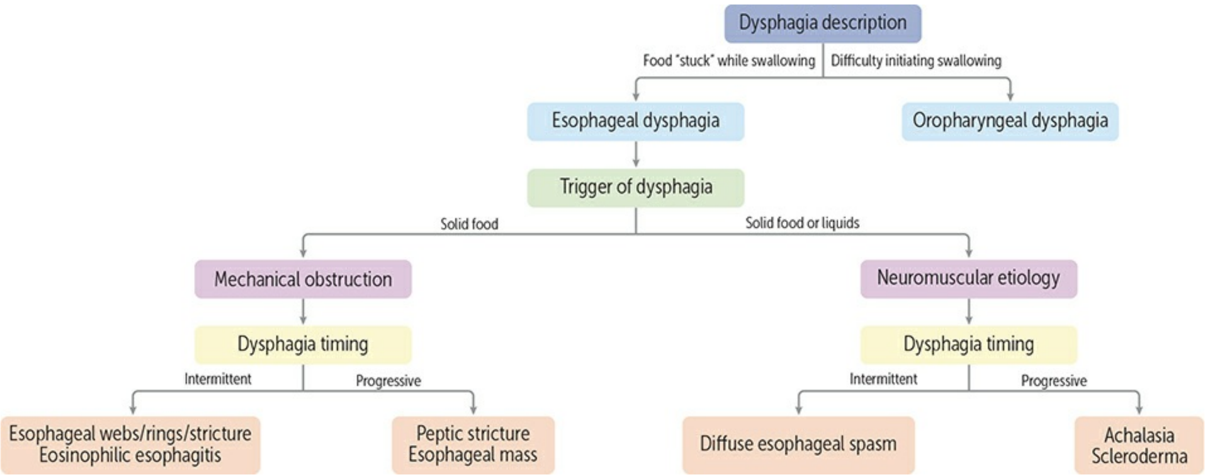

Dysphagia description
Food "stuck" while swallowing
Difficulty initiating swallowing
Esophageal dysphagia
Oropharyngeal dysphagia
Trigger of dysphagia
Solid food
Solid food or liquids
Mechanical obstruction
Neuromuscular etiology
Dysphagia timing
Dysphagia timing
Intermittent
Progressive
Intermittent
Progressive
Esophageal webs/rings/stricture
Eosinophilic esophagitis
Peptic stricture
Esophageal mass
Diffuse esophageal spasm
Achalasia
Scleroderma

FIGURE 2.6-3. Approach to differential diagnosis of esophageal dysphagia. (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

In an immunocompromised person with odynophagia, candidiasis should be one of the differential diagnoses.

Oropharyngeal Dysphagia

Problem with initiation of swallowing that may lead to aspiration of food into the lungs or regurgitation of food.

- **Etiology:** Neurologic or muscular, including stroke, Parkinson disease, myasthenia gravis, prolonged intubation, and Zenker diverticula.
- Usually more of a problem with liquids than with solids.

KEY FACT

Patients who are immunocompromised (eg, HIV) with odynophagia or dysphagia may be empirically treated for candida esophagitis. EGD can be considered if there is no response to diagnose other causes (eg, CMV or HSV esophagitis).

- **History/PE:** Rule out alternative syndromes such as xerostomia, globus, and esophageal dysphagia through history and physical examination.
- **Investigations:** Consider specific laboratory tests to rule out myopathies, myasthenia, or other conditions. Consider brain imaging if central nervous system (CNS) tumor, stroke, or head trauma is suspected.
- **Best initial test:** Modified barium swallow (video fluoroscopic swallowing exam) ± esophageal manometry. Esophagogastroduodenoscopy (EGD) may also be appropriate to rule out structural disease (see Fig. 2.6-3).
- **Treatment:** Diet modification, swallowing therapy, and sometimes temporary nonoral feeds. Severe dysphagia may require nonoral feeding (eg, percutaneous endoscopic gastrostomy) or tracheostomy. Structural causes must be treated specifically (eg, cricopharyngectomy and diverticulectomy for Zenker diverticula).

Esophageal Dysphagia

- Generally, patients complain that food gets “stuck” in the throat; however, there is no issue initiating swallowing.
- Can be caused by an obstruction (eg, strictures, Schatzki rings, webs, carcinoma) or motility disorder (eg, achalasia, scleroderma, esophageal spasm).
- Obstructions usually more of a problem with solids than with liquids; motility disorders cause both solid and liquid food dysphagia.
- **Best initial test:** EGD; consider pre-EGD barium swallow (aka esophagram) if history of esophageal radiation, caustic ingestion, esophageal or laryngeal cancer surgery, or strictures, as these patients may be at higher risk for esophageal perforation; this may be followed by manometry in some cases.

KEY FACT

Esophageal webs are associated with iron-deficiency anemia and glossitis (Plummer-Vinson syndrome).

INFECTIOUS ESOPHAGITIS

Inflammation of the esophageal lining. Seen in immunocompromised patients. Table 2.6-4 outlines the etiology, diagnosis, and treatment of infectious esophagitis.

TABLE 2.6-4. **Causes of Infectious Esophagitis**

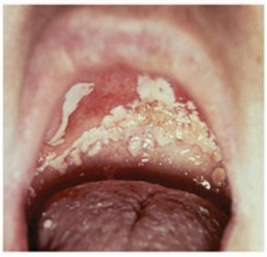
ETIOLOGIC AGENT	EXAM FINDINGS	UPPER ENDOSCOPY	TREATMENT
Candida albicans 	± oral thrush	Yellow-white plaques adherent to the mucosa; biopsy shows yeasts and hyphae invading mucosal cells	Fluconazole PO (treat with more than a topical agent alone)
Herpes simplex virus	Oral ulcers	Small, deep ulcerations with "volcano-like" appearance; multinucleated giant cells with intranuclear inclusions on biopsy + Tzanck smear	Acyclovir IV or PO
Cytomegalovirus	Retinitis, colitis	Large, linear, superficial ulcerations; intranuclear and intracytoplasmic inclusions on biopsy	Ganciclovir IV

Image reproduced with permission from Kantarjian HM, et al. *MD Anderson Manual of Medical Oncology.* New York: McGraw-Hill; 2006.

History

Commonly presents with odynophagia and/or dysphagia.

KEY FACT

Candida esophagitis is an AIDS-defining illness, typically when CD4+ cell count <100 cells/µL.

KEY FACT

High-risk factors for Candida esophagitis include broad-spectrum antibiotics, corticosteroids, treatment in an intensive care unit (ICU), cancer, diabetes, organ transplant, mechanical ventilation, and indwelling catheter.

PILL (MEDICATION-INDUCED) ESOPHAGITIS

Caused by ingestion of medications that have a direct toxic effect on the mucosa of the esophagus through creation of a localized acidotic or alkaline environment by the inciting medication.

Risk Factors

- Medication known to be associated with pill esophagitis (see related key fact)
- Taking medications without water or immediately before lying down

- Anything that might increase dwell time of medications in the esophagus (eg, geriatric-related low saliva production, altered esophageal anatomy, drinking insufficient water with medication, and motility disorders of the esophagus)

History/PE

- Dysphagia/odynophagia
- Retrosternal burning
- Taking an offending medication

Diagnosis

- Clinical diagnosis for patients with symptoms who took a medication known to cause pill esophagitis
- Upper endoscopic evaluation with biopsy for patients with severe symptoms (hematemesis, abdominal pain, weight loss) or symptoms that don't resolve after discontinuing the medication for at least 1 week
- Endoscopic evaluation usually reveals a localized ulceration of the esophagus with surrounding normal mucosa (see Fig. 2.6-4)

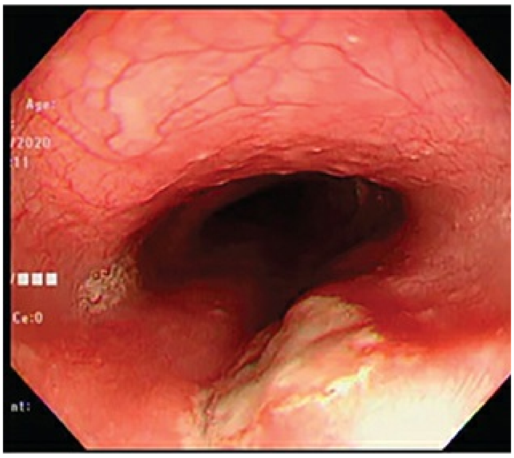


FIGURE 2.6-4. **An ulcer in the esophagus caused by nonsteroidal anti-inflammatory drugs (NSAIDs).** (Adapted with permission from Hu S-W, Chen A-C, Wu S-F. Drug-induced esophageal ulcer in adolescent population: Experience at a single medical center in central Taiwan. *Medicina*. 2021;57[12]:1286. https://doi.org/10.3390/medicina57121286.)

Treatment

- Discontinuing inciting medication (symptoms usually resolve in 7 to 10 days after discontinuation)
- If medication cannot be discontinued, switching to liquid formulation

EOSINOPHILIC ESOPHAGITIS

Immune-mediated disorder of the esophagus in which eosinophils are recruited to the esophagus causing dysphagia or food impaction.

History/PE

- Past medical history of seasonal allergies and asthma
- Presents with dysphagia, food impaction, centrally located chest pain not relieved by proton pump prohibitors (PPIs)

Diagnosis

- Diagnosis is based on clinical presentation and evaluation with EGD and esophageal biopsy
- EGD most commonly shows ringlike structures (44%) or thickened linear furrows (48%) (see Fig. 2.6-5)

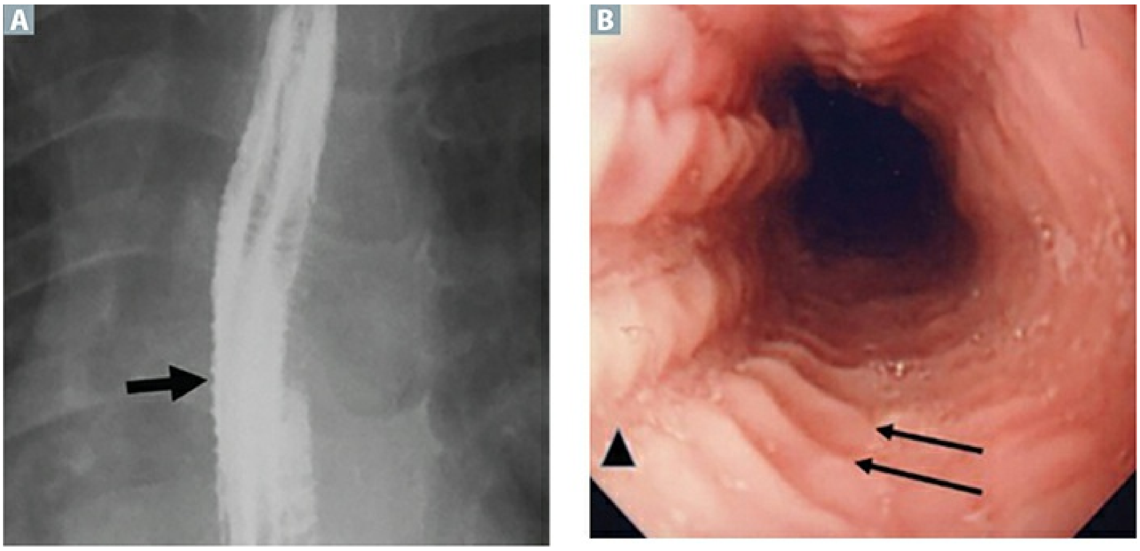


FIGURE 2.6-1. **Concentric rings.** Mucosal irregularity (**A:** black arrow) and furrows (**B:** black arrowhead) seen in esophagus with eosinophilic esophagitis on fluoroscopic evaluation **(A)** and endoscopic evaluation **(B)**. (Images modified with permission from Al-Hussaini A, AboZeid A, Hai A. How does esophagus look on barium esophagram in pediatric eosinophilic esophagitis? Abdom Radiol (NY). 2016;41[8]:1466-1473.)

- Biopsy is the most accurate test and will reveal esophageal inflammation with an eosinophilic-predominant infiltrate (≥15 eosinophils per high-powered field on light microscopy)

KEY FACT

Common causes of pill esophagitis include antibiotics (especially tetracyclines), nonsteroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, ascorbic acid, potassium chloride, ferrous sul-fate, acetaminophen, warfarin, and chemotherapy regimens.

Treatment

- **Best initial treatment:** PPIs and elimination of possible causes (ie, six-food elimination diet involving exclusion of wheat, milk, egg, nuts, soy, and fish/shellfish).
- If initial treatment fails, swallowed inhalational steroids or swallowed topical steroids are recommended for further management.
- Esophageal dilation may be required in refractory disease.

ESOPHAGEAL RINGS

Concentric “ring” of tissue protruding into the esophageal lumen. Most commonly seen in the distal esophagus. Often associated with another condition (eg, eosinophilic esophagitis and hiatal hernia). Schatzki rings are the most common type of esophageal ring. In Figure 2.6-5, rings are shown on fluoroscopic evaluation (A) and endoscopic evaluation (B).

History/PE

Patients with esophageal rings are usually asymptomatic, but they may present with dysphagia to solids. With more chewing, symptoms tend to be less severe. Increased severity of symptoms is associated with internal diameter of esophageal lumen associated with ring.

Diagnosis

- **Barium swallow:** Thin, symmetric, circumferential narrowing
- **EGD and biopsy:** Thin, smooth, circumferential membrane; biopsy used to evaluate for esophagitis

Treatment

Goal of therapy is to relieve symptoms if present and prevent recurrent symptoms.

- **Initial therapy:** Esophageal dilation followed by 6 weeks of PPI therapy
- **Recurrent and refractory symptoms:** Repetition of EGD to confirm absence of eosinophilic esophagitis (can be patchy) and repetition of esophageal dilation + addition of long-term PPI.

KEY FACT

Steakhouse syndrome refers to food impaction of the esophagus after eating a piece of food without sufficient chewing. This most often involves a meat bolus. Steakhouse syndrome must be differentiated from other causes of dysphagia.

PLUMMER-VINSON SYNDROME

History/PE

Plummer-Vinson syndrome presents with a classic triad of dysphagia, iron-deficiency anemia (fatigue and weakness), and esophageal webs. Additional findings may include glossitis, angular cheilitis, koilonychia, splenomegaly, and thyromegaly. Figure 2.6-6 shows a radiographic view of an esophageal web.

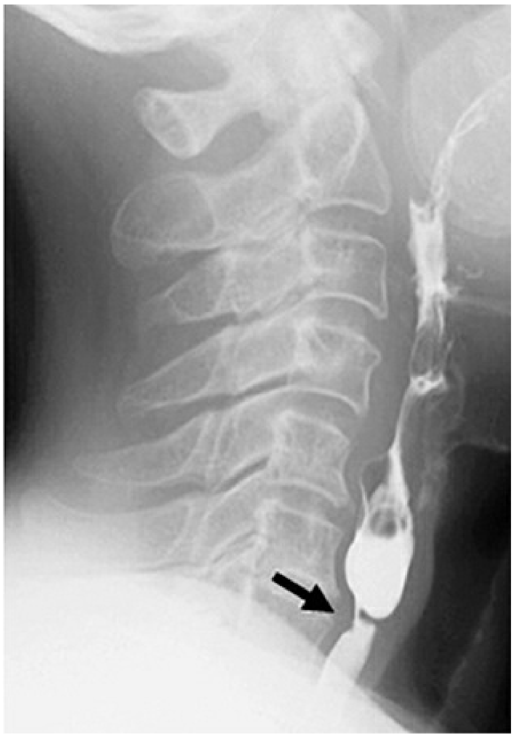


FIGURE 2.6-6. **Radiographic evaluation revealing an esophageal web.** (Reproduced with permission from Ohtaka M, Kobayashi S, Yoshida T, et al. Use of Sato's curved laryngoscope and an insulated-tip knife for endoscopic incisional therapy of esophageal web. *Dig Endosc.* 2015 May;27(4):522-526. doi: 10.1111/den.12334.)

Diagnosis

Laboratory testing reveals iron-deficiency anemia, and an esophageal web appears on esophagram, videofluoroscopic evaluation, or upper endoscopy.

Treatment

- **Iron repletion:** Rapid resolution of dysphagia in some patients
- **Esophageal dilation:** May be necessary in those with significant esophageal lumen obstruction
- **Annual upper endoscopy + biopsy:** Recommended by some to watch for development of SCC, although no change in outcomes has been observed in the literature with this screening

KEY FACT

Esophageal webs are like esophageal rings, but they are noncircumferential and are associated with different conditions (eg, Plummer-Vinson syndrome, which occurs in patients with long-term iron-deficiency anemia). Esophageal webs are often ruptured during EGD and do not cause recurrent or refractory symptoms.

MNEMONIC

Plumbers DIE from Plummer-Vinson syndrome:

Dysphagia
Iron-deficiency anemia

Esophageal web

DISTAL ESOPHAGEAL SPASM

Motility disorder in which normal peristalsis is periodically interrupted by high-amplitude, nonperistaltic contractions (see Fig. 2.6-7A).

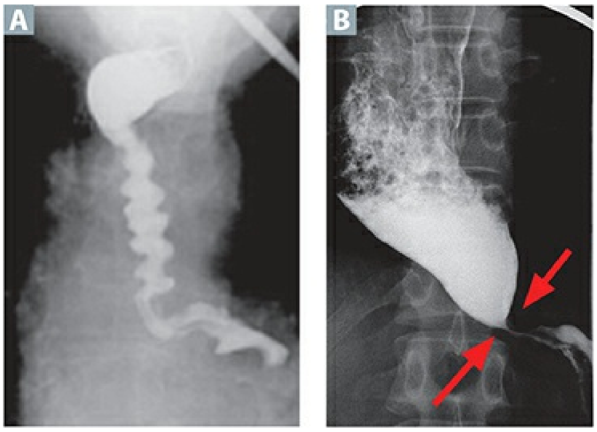


FIGURE 2.6-7. **Esophageal disease on barium esophagram. (A)** Esophageal spasm. **(B)** Achalasia. Note the dilated esophagus tapering to a "bird's beak" narrowing *(arrows)* at the LES. (Image A reproduced with permission from USMLE-Rx.com. Image B reproduced with permission from Doherty GM. *Current Diagnosis & Treatment: Surgery*. 13th ed. New York, NY: McGraw-Hill; 2010.

History/PE

Presents with heartburn, chest pain, dysphagia, and odynophagia. Often precipitated by ingestion of hot or cold liquids; relieved by nitroglycerin.

KEY FACT

The musculature of the upper one-third of the esophagus is skeletal, whereas that of the lower two-thirds is smooth muscle.

Diagnosis

- **EGD with biopsy:** Best initial test to rule out other esophageal disorders.
- **Barium swallow:** Shows a corkscrew-shaped esophagus. Done as initial test prior to EGD in selected patients at risk of perforation (proximal esophageal lesion [eg, Zenker diverticulum, radiation therapy], known complex strictures [due to radiation exposure or caustic injury]).
- **Most accurate test:** Esophageal manometry, which allows for definitive diagnosis. High-amplitude, simultaneous contractions shown in greater than 20% of swallows.

Treatment

- **Symptomatic relief:** Calcium channel blockers, tricyclic antidepressants (TCAs), or nitrates
- **Severe, incapacitating symptoms:** Growing evidence supporting peroral endoscopic myotomy (POEM)

ACHALASIA

Motility disorder of the esophagus characterized by impaired relaxation of the lower esophageal sphincter (LES) and loss of peristalsis in the distal two-thirds of the esophagus.

Etiology

Degeneration of the inhibitory neurons in the myenteric (Auerbach) plexus.

History/PE

Progressive dysphagia (solids and liquids), chest pain, regurgitation of undigested food, weight loss, and nocturnal cough.

Diagnosis

- **Best initial test:** EGD to rule out structural disorders, including mechanical obstruction, pseudoachalasia, cancer.
- **Most accurate test:** High-resolution manometry, which shows increase in resting LES pressure, incomplete LES relaxation upon swallowing, and decrease in peristalsis in the body of the esophagus (see Fig. 2.6-8).

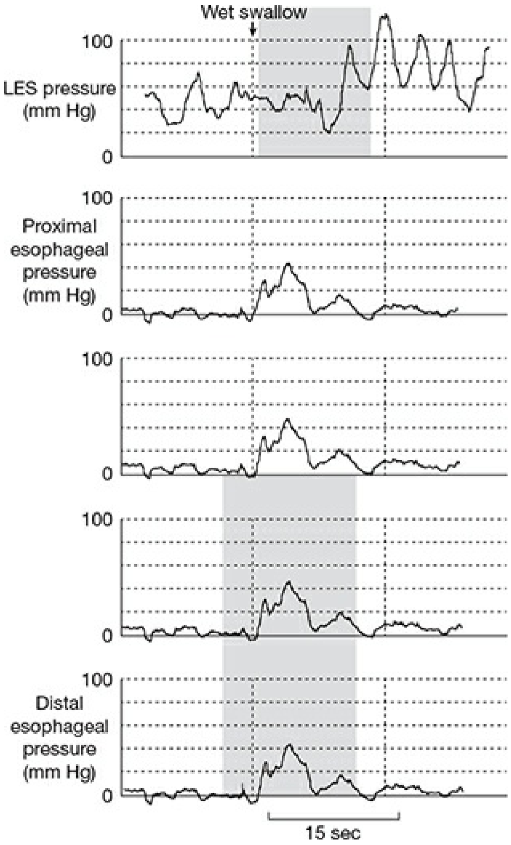


FIGURE 2.6-8. **Achalasia.** Manometry with incomplete LES relaxation. (Reproduced with permission from Farrokhi F, Vaezi MF. Idiopathic (primary) achalasia. *Orphanet J Rare Dis.* 2007;2:38.)

- Barium swallow is useful when manometric findings are equivocal. Will show esophageal dilation with "bird's beak" tapering of the distal esophagus (see Fig. 2.6-7B).

Treatment

- **Definitive:** First-line treatment options are laparoscopic Heller myotomy, POEM, and less often, pneumatic dilation.

- If first-line options are unsuitable, the physician may administer injection of botulinum toxin.
- Calcium channel blockers and phosphodiesterase inhibitors or nitrates may provide short-term relief. They are only used in patients who are not candidates for definitive therapy and have failed botulinum toxin injection.

ESOPHAGEAL DIVERTICULA

Diverticula can be present in any location in the esophagus or pharynx. Usually due to distal stricture/stenosis leading to increased pressure in the proximal esophagus. Zenker diverticulum is a cervical outpouching through the cricopharyngeus muscle. It is a posterior, false diverticulum (outpouching only through submucosa and mucosa). See Figure 2.6-9.

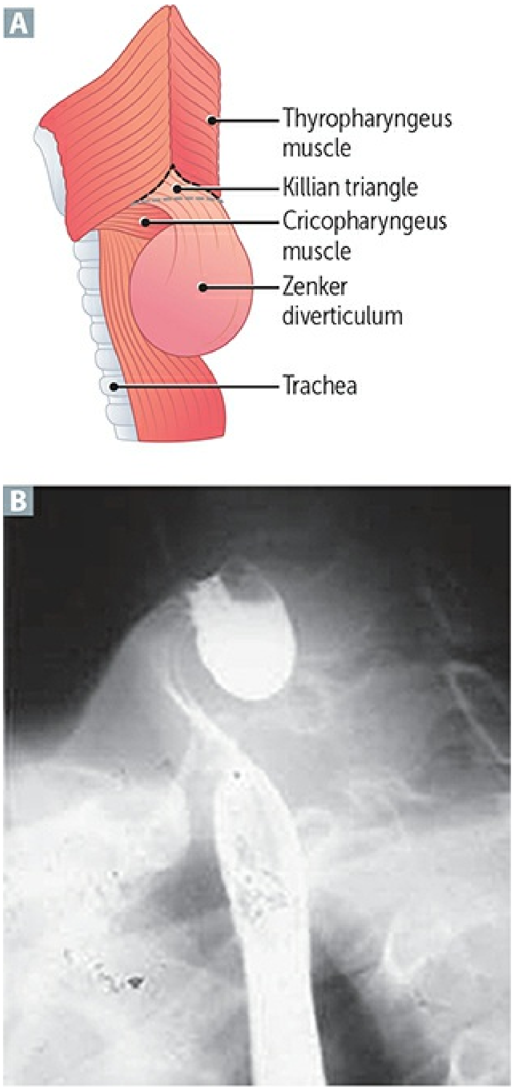


FIGURE 2.6-9. **Illustration of a Zenker diverticulum (A) and fluoroscopic evaluation revealing a Zenker diverticulum (B).** (Image A reproduced with permission from USMLE-Rx.com. Image B reproduced with permission from Dionigi G, Sessa F, Rovera F, et al. Ten year survival after excision of squamous cell cancer in Zenker's diverticulum: report of a case. *World J Surg Oncol.* 2006;4:17. doi:10.1186/1477-7819-4-17.)

- ***Hx/PE:*** Chest pain, dysphagia, halitosis, and regurgitation of undigested food.
- ***Dx:*** Barium swallow to demonstrate outpouchings.

- ***Tx:*** If symptomatic, surgical excision of the diverticulum. For Zenker diverticulum, myotomy of the cricopharyngeus required to relieve the high-pressure zone.

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) is symptomatic reflux of gastric contents into the esophagus, most commonly from transient LES relaxation. Incompetent LES, gastroparesis, or hiatal hernia can all contribute to GERD, but they are not the sole causes. Figure 2.6-10 depicts the general management approach to GERD-like symptoms.

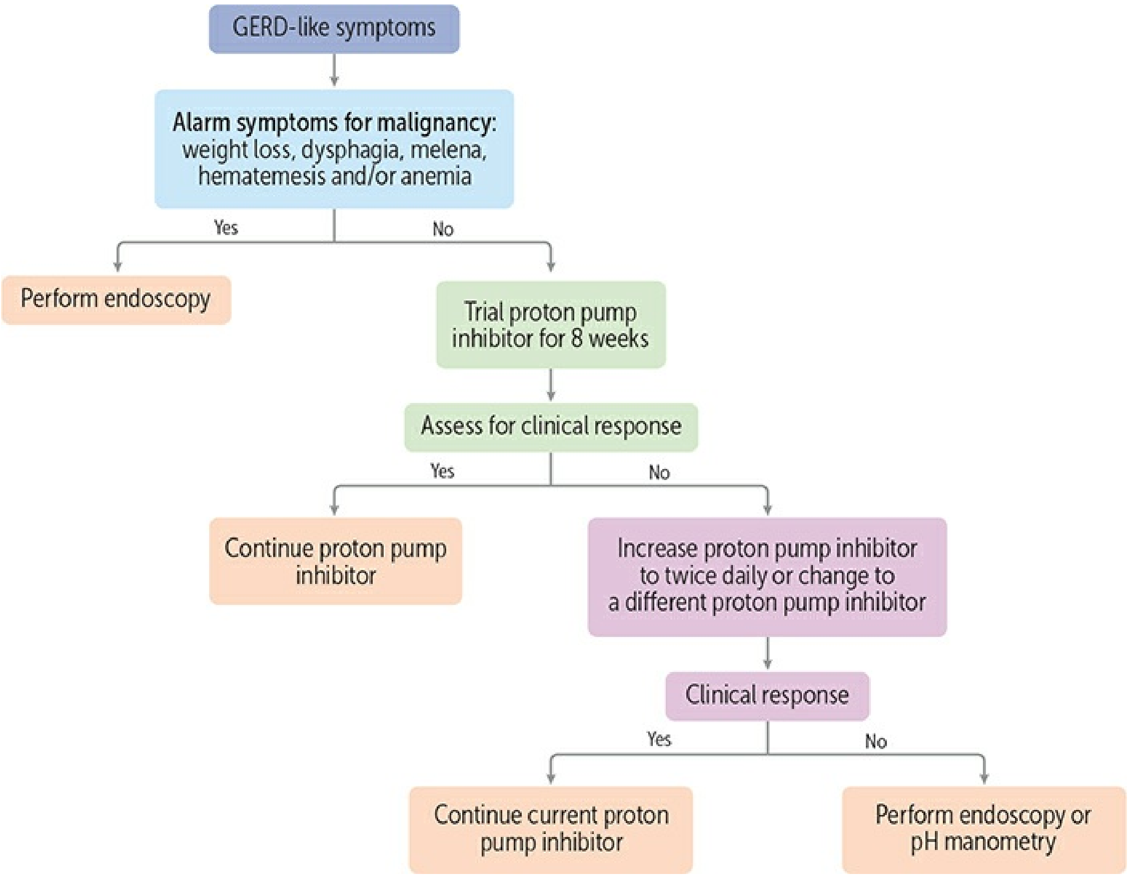

GERD-like symptoms
Alarm symptoms for malignancy: weight loss, dysphagia, melena, hematemesis and/or anemia
Yes
No
Perform endoscopy
Trial proton pump inhibitor for 8 weeks
Assess for clinical response
Yes
No
Continue proton pump inhibitor
Increase proton pump inhibitor to twice daily or change to a different proton pump inhibitor
Clinical response
Yes
No
Continue current proton pump inhibitor
Perform endoscopy or pH manometry

FIGURE 2.6-10. **Management of GERD-like symptoms.** (Reproduced with permission from USMLE-Rx.com.)

History/PE

- Heartburn and/or regurgitation that commonly occurs 30 to 90 minutes after a meal; worsens with reclining; and often improves with antacids, sitting, or standing. Uncommon symptoms: sour taste, a globus sensation, unexplained cough, morning hoarseness, and chest pain mimicking coronary artery disease.
- Normal unless a systemic disease (eg, scleroderma) is present.

Diagnosis

- Primarily a clinical diagnosis, with empirical treatment first in patients without alarm symptoms (see later for lifestyle modification and medical treatment).
- **Most accurate test:** 24-hour pH monitoring with impedance; indicated if the diagnosis is uncertain.
- **EGD with biopsy:** Performed in patients whose symptoms are the following:

  - Refractory to initial empiric therapy
  - Long-standing (to rule out Barrett esophagus and adenocarcinoma; see Fig. 2.6-11)

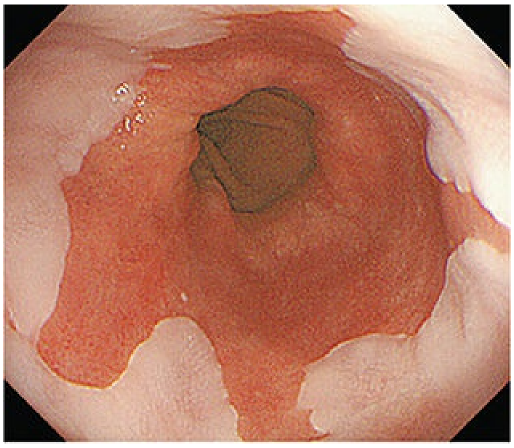


FIGURE 2.6-11. **Barrett esophagus on upper endoscopy.** Shown is proximal extension of Z-line (squamocolumnar junction between esophagus and stomach) caused by columnar metaplasia. The squamocolumnar junction must extend at least 1 cm above the gastroesophageal junction to diagnose Barrett's esophagus. (Reproduced with permission from Fauci AS et al. *Harrison's Principles of Internal Medicine*, 17th ed. New York, NY: McGraw-Hill; 2008.)

- Associated with alarm symptoms like hematemesis, weight loss, dysphagia/odynophagia, or chest pain. ECG (or cardiac referral) should be done first.
- **Other studies:** Indicated for refractory symptoms or if concern for other causes. May include esophageal manometry. Although barium swallow may demonstrate reflux, its role is limited due to a high prevalence of physiologic reflux.

KEY FACT

GERD can mimic angina or myocardial infarction.

KEY FACT

GERD is not a result of the presence of *Helicobacter pylori*. GERD arises from a transient relaxation of the LES.

Treatment

- **Lifestyle modifications:** Indicated for all patients, these modifications include weight loss; head-of-bed elevation; small meals; avoidance of nocturnal meals; avoidance of substances like alcohol, chocolate, or coffee that ↓ LES tone.
- An initial, empirical trial of pharmacotherapy (eg, 8 weeks of PPI) is indicated in patients with clinical features of GERD in the absence of alarm symptoms.
- In the presence of alarm symptoms (weight loss, dysphagia, and gastrointestinal [GI] bleeding) and in patients with multiple risk factors for Barrett esophagus, endoscopy should be performed initially (ie, before trial of PPI).
- Pharmacologic treatment:
  - **Mild/intermittent:** Antacids
  - **Chronic/frequent:** H_2-receptor antagonists (cimetidine, famotidine) or PPIs

    (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, dexlansoprazole). Fundoplication surgery or other antireflux procedures may benefit carefully selected patients.
  - **Severe/erosive:** PPIs first; fundoplication surgery or other antireflux procedures may benefit carefully selected patients.
- **Complications:** Erosive esophagitis, esophageal peptic stricture, aspiration pneumonia, upper GI bleeding, Barrett esophagus, adenocarcinoma.
- **Management of Barrett esophagus:** Optimization of medical therapy (should be on chronic PPI therapy). Based on biopsy findings, management calls for the following steps:
  - No dysplasia: Repeat endoscopy every 3 to 5 years
  - Indefinite dysplasia: Repeat endoscopy in 2 to 6 months
  - Dysplasia or intramucosal carcinoma: Treat with endoscopic eradication
  - Esophageal adenocarcinoma: See Esophageal Cancer section of this chapter for treatment.

HIATAL HERNIA

Herniation of stomach upward into the chest through the diaphragm. Common types:

- **Sliding hiatal hernia (95%):** Gastroesophageal junction and a portion of the proximal stomach are displaced above the diaphragm (see Fig. 2.6-12).

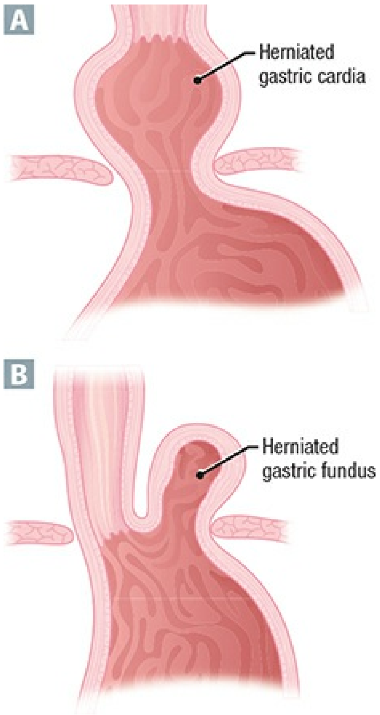


FIGURE 2.6-12. **(A) Sliding hiatal and (B) paraesophageal hiatal hernia.** (Reproduced with permission from USMLE-Rx.com.)

- **Paraesophageal hiatal hernia (5%):** Gastroesophageal junction remains below the diaphragm while the fundus herniates into the thorax (see Fig. 2.6-12).
- ***Hx/PE:*** Most are asymptomatic. Patients with sliding hernias may present with GERD; paraesophageal hernias can cause strangulation.
- ***Dx:*** Incidental finding is apparent on CXR; it is also frequently diagnosed by barium swallow or EGD.

- *Tx:*
  - **Sliding hernias:** Medical therapy and lifestyle modifications to ↓ GERD symptoms
  - **Paraesophageal hernias:** Surgical gastropexy to prevent gastric volvulus in some cases

ESOPHAGEAL CANCER

SCC is the most common type of esophageal cancer worldwide. Adenocarcinoma is the most common type of esophageal cancer in the United States, Europe, and Australia.

Risk Factors

- **SCC:** Alcohol use, tobacco use, and nitrosamines
- **Adenocarcinoma:** Barrett esophagus (intestinal metaplasia of the distal esophagus secondary to chronic GERD)

KEY FACT

SCC of the esophagus tends to occur in the upper and middle thirds of the esophagus, whereas adenocarcinoma occurs in the lower third.

History/PE

Progressive dysphagia—initially to solids and later to liquids—is common. Weight loss, odynophagia, GERD, GI bleeding, and vomiting are also seen.

Diagnosis

- **Best initial and most accurate test:** EGD + biopsy; required to establish diagnosis
- CT and endoscopic ultrasound (EUS) for tumor staging

KEY FACT

No radiologic test can diagnose esophageal cancer. Diagnosis must be made with a tissue biopsy.

KEY FACT

Esophageal cancer metastasizes early, because the esophagus lacks a serosa.

Treatment

- **Best initial treatment:** Chemoradiation and surgical resection. If there is metastatic disease that is considered incurable, systemic therapy alone is used.
- Resection is also indicated in cases of high-grade Barrett dysplasia
- Has a poor prognosis

KEY FACT

Resection is required for esophageal cancer treatment to be curative.

KEY FACT

One unit of packed RBCs should ↑ hemoglobin by 1 g/dL and hematocrit by 3 to 4 units.

GASTROINTESTINAL BLEEDING

Overt GI bleeding presents as hematemesis, hematochezia, and/or melena. Bleeding may be from the upper GI tract (ie, bleeding from lesions proximal to the ligament of Treitz, the anatomic boundary between the duodenum and jejunum) or from the lower GI tract. Table 2.6-5 presents the features of upper and lower GI bleeding, and this chapter discusses selected conditions.

TABLE 2.6-5. Features of Upper and Lower GI Bleeding

VARIABLE	UPPER GI BLEEDING	LOWER GI BLEEDING
History/exam	Hematemesis ("coffee-ground" emesis), melena > hematochezia, hypovolemia (eg, elevated blood urea nitrogen [BUN], tachycardia, lightheadedness, hypotension)	Hematochezia > melena, but can be either
Diagnosis	Nasogastric (NG) tube and lavage (may be ⊖ in 15% of upper GI bleeds); endoscopy is definitive	Rule out upper GI hemorrhage with NG lavage if brisk Anoscopy/sigmoidoscopy for patients <45 years of age with small-volume bleeding Colonoscopy if stable; arteriography or exploratory laparotomy if unstable
Etiologies	Peptic ulcer disease ([PUD] most common), esophagitis/gastritis, Mallory-Weiss tear, esophageal/gastric varices, gastric antral vascular ectasia, malignancy, Dieulafoy lesions	Diverticulosis (60%), angiodysplasia, IBD, hemorrhoids/fissures, neoplasm, arteriovenous malformation
Initial management	Protect the airway (intubation may be needed). Place two large-bore IVs; immediately administer fluids and transfusions if hemoglobin <8 g/dL (packed RBCs [hematocrit may be normal early in acute blood loss], platelets, or fresh frozen plasma as indicated)	Stabilize the patient with IV fluids and packed RBCs (hematocrit may be normal early in acute blood loss)
Long-term management	Endoscopy followed by therapy directed at the underlying cause	Depends on the underlying etiology. Endoscopic therapy (eg, epinephrine injection, cauterization, or clip placement), intra-arterial vasopressin infusion or embolization, or surgery for diverticular disease or angiodysplasia

UPPER GI BLEEDING

Esophageal and Gastric Varices

Etiology

- Esophageal and gastric varices stem from increases in portal pressure, which result in collateral flow of blood from the portal circulation into the systemic circulation via portosystemic shunts that increase esophageal venous blood flow. This may result in dilated esophageal veins (ie, esophageal varices) that are prone to bleeding.

- The most common reason for increased portal pressure is hepatic cirrhosis (due to alcohol abuse or viral hepatitis). Other causal conditions include right heart failure and hepatic vein obstruction (Budd-Chiari syndrome). See Figure 2.6-13 for endoscopic images of esophageal varices.

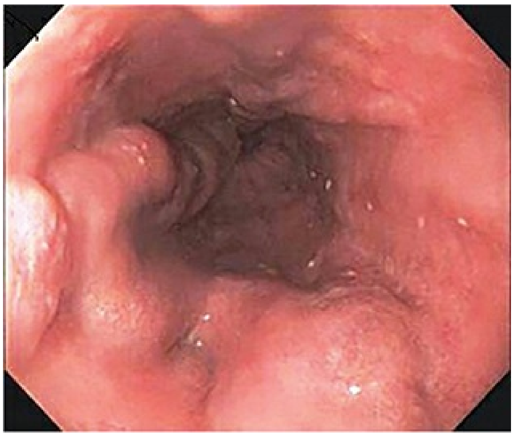


FIGURE 2.6-13. **Esophageal varices seen on upper endoscopy.** (Adapted with permission from Akiyama T, Abe Y, Iida H, et al. Endoscopic therapy using an endoscopic variceal ligation for minute cancer of the esophagogastric junction complicated with esophageal varices: A case report. *J Med Case Rep.* 2010;4:149.)

History/PE

- Painless GI bleeding manifesting as hematemesis or melena (less commonly hematochezia)
- Possible signs and symptoms of cirrhosis such as jaundice, pruritis, hepatic encephalopathy (altered mental status), asterixis, palmar erythema, caput medusa, and spider angiomas

Diagnosis and Treatment

- **Initial treatment** for upper GI bleeding includes hemodynamic stabilization and transfusion (packed RBCs, fresh frozen plasma, or platelets as indicated). Additionally, acid suppression (IV PPI reduces rebleeding rate and need for blood transfusion for ulcers) and prokinetic agents (erythromycin or metoclopramide improve visualization when endoscopy is performed) are given.
- Treatment specific for suspected variceal bleeding includes antibiotic prophylaxis for spontaneous bacterial peritonitis (eg, ceftriaxone) and vasoactive agents (octreotide).
- Control of bleeding may be achieved with upper GI endoscopy (endoscopic variceal ligation or sclerotherapy), which should be performed within 12 hours. This also confirms the diagnosis.
- A transjugular intrahepatic portosystemic shunt (TIPS) may be required if endoscopic treatment fails or there is a high risk of rebleeding. Rarely, temporary treatments may be used in the interim until TIPS can be done (esophageal stent or balloon tamponade). Later sections of this chapter give more information on TIPS.

KEY FACT

Although upper GI endoscopy may confirm the diagnosis in acute upper GI bleeding, the best initial step is to stabilize the patient hemodynamically with fluids and transfusion, and ensure the airway is protected.

Other Causes of Upper GI Bleeding

Mallory-Weiss tear: Forced retching causes longitudinal intramural lacerations of the esophagus resulting in bleeding from the submucosa. Common causes: bulimia, alcohol use disorder, coughing, and hiccups.

- ***Dx/Tx:*** Diagnosis and treatment to stop bleeding are established on upper GI endoscopy. Many spontaneously resolve, and low-risk patients may be treated as outpatients. They may require fluid resuscitation, antiemetics, and endoscopic hemostasis, depending on presentation.

Boerhaave syndrome: Rupture of the esophagus causes vomiting or straining (increased intraesophageal pressure and decreased intrathoracic pressure).

- ***Hx/PE:*** Patients have retrosternal chest pain and crepitus. Sometimes there may be neck or back pain, upper abdominal pain, hoarseness of voice, dysphagia, or odynophagia. Patients deteriorate in hours and develop dyspnea, sepsis, and shock.
- ***Dx:*** Contrast esophagogram or CT scan confirm the diagnosis. CXR may show mediastinal, subdiaphragmatic, or free peritoneal air; subcutaneous emphysema; pleural effusions; mediastinal widening; and other changes. However, it has low sensitivity.
- ***Tx:***
  - Nothing by mouth (NPO), IV fluids, nutritional support, broad-spectrum antibiotics, PPI.
  - Free or large perforations in high-risk patients are handled with surgery or esophageal stenting (if surgery contraindicated). Contained or small perforations may not require surgery.

Dieulafoy lesion: An anatomic variant of a submucosal arteriole in the stomach wall. See Figure 2.6-14 for an endoscopic view of Dieulafoy lesion.

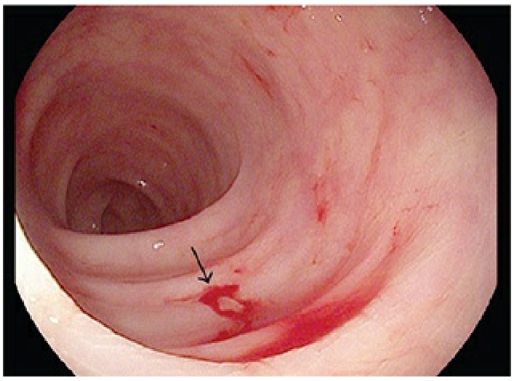


FIGURE 2.6-14. **Endoscopic image of Dieulafoy lesion of the colon.** (Adapted with permission from Ma C, Hundal R, Cheng EJ. Colonic Dieulafoy's lesion: A rare cause of lower gastrointestinal hemorrhage and review of endoscopic management. *Case Rep Gastrointest Med.* 2014;2014:436293.)

- ***Hx/PE:*** Patients will present with painless bleeding from an unidentifiable source, and the condition can be either brisk or self-limited (yet prone to recur). NSAID use is typical and may incite bleeding.
- ***Dx:*** EGD with visualization of bleeding or angiogram.
- ***Tx:*** Electrocoagulation during endoscopy is common, although many other options can effectively treat this condition (eg, clips or epinephrine injection).

DISORDERS OF THE STOMACH AND DUODENUM

DYSPEPSIA

Commonly experienced; range of symptoms typically characterized by upper abdominal discomfort and/or pain after eating.

History/PE

After eating or drinking, patients may experience early satiety, bloating, and/or epigastric pain or discomfort. Patient history suggests possible etiologies, although few patients will have an identifiable, underlying cause. However, history is important to consider when thinking of next best test.

- **Malignancy:** History of smoking and obstructive or constitutional symptoms (eg, weight loss, night sweats, chills)
- **Peptic ulcer disease (PUD):** Pain and discomfort localized to epigastric area
- **Drug induced:** Symptoms coinciding with initiation of new drug (eg, NSAIDs, bisphosphonates, antibiotics)
- **Biliary:** Episodic pain localized to the right upper quadrant

Diagnosis

Per Rome IV criteria, the diagnosis of functional dyspepsia is made when there is no evidence of structural disease and one or more of the following:

- Bothersome postprandial fullness or early satiety
- Bothersome epigastric pain or burning

When ruling out secondary dyspepsia:

- If >60 years of age, all patients should undergo endoscopy
- If <60 years of age, only patients with "red flag" symptoms should have endoscopy

Other etiologies should be pursued, based on patient-specific history. In absence of symptoms specific to a discussed etiology, consider Helicobacter pylori testing.

KEY FACT

Red flag symptoms of dyspepsia: progressive dysphagia, iron-deficiency anemia, odynophagia, palpable mass or lymphadenopathy, persistent vomiting, or a family history of GI malignancy.

Treatment

Secondary causes should be treated with their respective therapies. However, if an identifiable cause is not found and the patient is negative for *H pylori*, patients may start PPI.

GASTRITIS

Inflammation of the gastric mucosa. See Figure 2.6-15 for general diagnostic approach to gastritis. Subtypes:

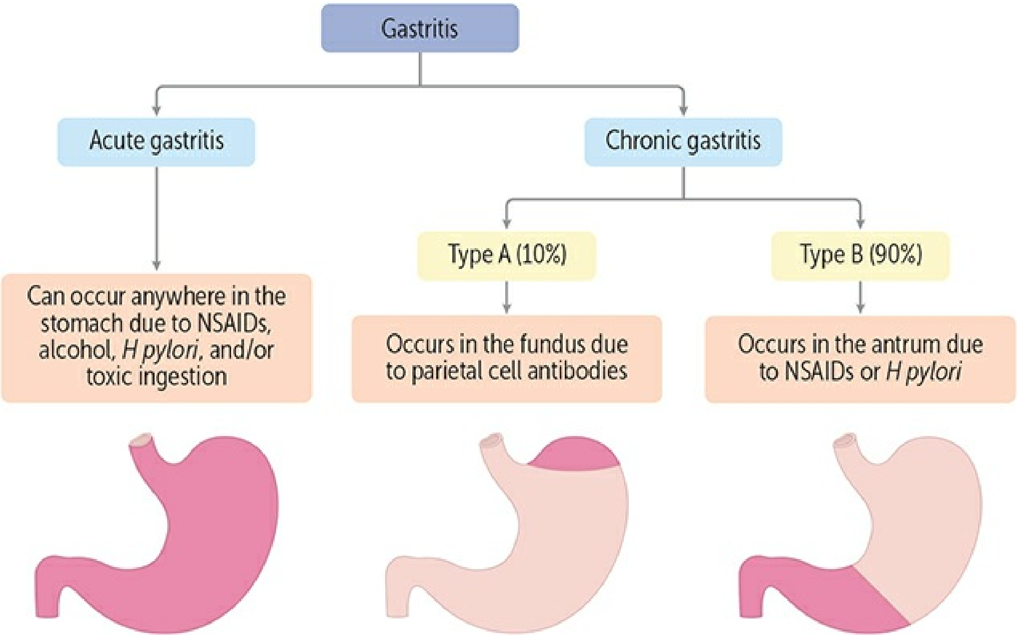

Gastritis
Acute gastritis
Chronic gastritis
Type A (10%)
Type B (90%)
Can occur anywhere in the stomach due to NSAIDs, alcohol, H pylori, and/or toxic ingestion
Occurs in the fundus due to parietal cell antibodies
Occurs in the antrum due to NSAIDs or H pylori

FIGURE 2.6-15. **General diagnostic approach to gastritis.** (Reproduced with permission from USMLE-Rx.com.)

- **Acute gastritis:** Rapidly developing, superficial, or deep erosive lesions, often caused by NSAIDs, alcohol, H pylori infection, and stress from severe illness (eg, burns, CNS injury). Toxic ingestion can also cause acute gastritis, along with possible gastric outlet stricture.
- **Chronic gastritis:**
  - **Type A (10%):** Occurs in the fundus and is caused by autoantibodies to parietal cells. Causes pernicious anemia and is associated with other autoimmune disorders and ↑ risk for gastric adenocarcinoma and carcinoid tumors.
  - **Type B (90%):** Occurs in the antrum and may be caused by NSAIDs or *H pylori* infection. Often asymptomatic but associated with ↑ risk for PUD and gastric cancer. Note: *H pylori* infection can, but does not always, cause gastritis.

KEY FACT

Type A gastritis is associated with pernicious anemia caused by lack of intrinsic factor necessary for the absorption of vitamin B_{12}.

KEY FACT

H pylori antibodies stay ⊕ even when the infection is cleared. The urea breath test or a repeat stool antigen can serve as a test of cure.

KEY FACT

Stress ulcers include Curling ulcers, which are associated with burn injuries, and Cushing ulcers, which are associated with traumatic brain injury.

KEY FACT

Peptic ulcer disease and gastritis should be considered in older adult patients who are taking medications for arthritis or heart disease (eg, NSAIDs) and who present with abdominal pain or GI bleeding.

History/PE

Asymptomatic or symptomatic with epigastric pain, nausea, vomiting, hematemesis, or melena.

Diagnosis

Upper endoscopy is required to diagnose gastritis. Different tests for *H pylori* are shown in Table 2.6-6.

TABLE 2.6-6. Tests for *H pylori*

TEST	DESCRIPTION	TEST CHARACTERISTICS
Urea breath test	*H pylori* urease converts radio-labeled urea (C14 or C13) to CO_2 and ammonia; this test detects CO_2 formed from urea metabolism	High specificity, lower sensitivity PPIs may cause false ⊖ results
Stool antigen test	Stool antigen test detects *H pylori* antigens in stool	High specificity, high sensitivity Cost-effective initial test for *H pylori* Must be off PPI ×2 weeks prior to testing
Endoscopic biopsy	Endoscopic biopsy detects *H pylori* on histology or culture; it can also detect intestinal metaplasia, mucosa-associated lymphoid tissue (MALT), or widespread gastritis	Gold standard for diagnosis of gastritis and *H pylori* Most invasive test Must be off PPI ×2 weeks prior to endoscopy

Treatment

- Patient should stop intake of exacerbating agents such as NSAIDs or alcohol.
- Antacids, sucralfate, H_2 receptor blockers, and/or PPIs may help.
- Bismuth quadruple therapy (PPI, bismuth subcitrate, tetracycline, and metronidazole) can treat *H pylori* infection. Other quadruple regimens include PPI, clarithromycin, amoxicillin, and metronidazole.
- Patients at risk for stress ulcers (eg, intensive care unit [ICU] patients) should receive prophylactic PPIs.

KEY FACT

A gastric adenocarcinoma that metastasizes to the ovary is called a Krukenberg tumor.

GASTRIC CANCER

Malignant tumor (mostly adenocarcinoma) with a poor prognosis that is particularly common in Korea and Japan. See Fig. 2.6-16 for pathologic specimens of gastric cancer.

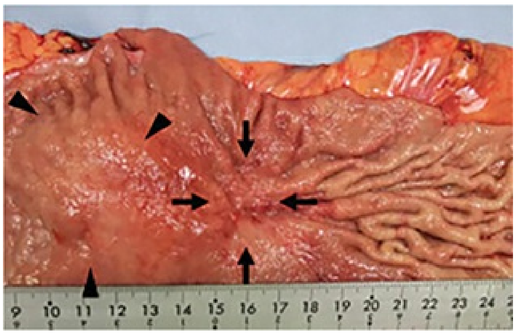


FIGURE 2.6-16. **Gastric ulcer subsequently diagnosed as adenocarcinoma.** (Adapted with permission from Kinoshita H, Yamaguchi S, Sakata Y, et al. A rare case of xanthogranuloma of the stomach masquerading as an advanced stage tumor. *World J Surg Oncol.* 2011;9:67.)

- ***Risk factors:*** Diet high in nitrites and salt and low in fresh vegetables (antioxidants), *H pylori* colonization, and chronic gastritis.
- ***Hx/PE:*** Early-stage disease usually asymptomatic, but may be associated with indigestion and loss of appetite.
  - Late-stage disease indicated by alarm symptoms: abdominal pain, weight loss, and upper GI bleeding.
- ***Dx:*** Upper endoscopy with biopsy (most accurate test) to rule out other etiologies and confirm the diagnosis.
- ***Tx:*** If detected early, surgical resection often with perioperative chemotherapy. Most patients present with late-stage, incurable disease. Systemic therapies are used for metastatic or incurable disease. Five-year survival rate is <10% for advanced disease.

KEY FACT

Mucosa-associated lymphoid tissue (MALT) lymphoma is a rare gastric tumor that presents in patients with chronic *H pylori* infection. It is the only malignancy that can be cured with antibiotics. The physician should treat it with triple therapy.

KEY FACT

Gastric cancer may present with a Virchow node (an enlarged left supraclavicular lymph node) or a Sister Mary Joseph node (a palpable lymph node near the umbilicus).

PEPTIC ULCER DISEASE

- Results from damage to the gastric or duodenal mucosa caused by impaired mucosal defense and/or ↑ acidic gastric contents.
- **Risk factors:** *H pylori* (>90% of duodenal ulcers and 70% of gastric ulcers), NSAIDs, alcohol and tobacco use; concomitant use of corticosteroids and NSAIDs; male sex

History/PE

- **Presentation:** Chronic or periodic dull, burning epigastric pain that is often related to meals and can radiate to the back; nausea; hematemesis (“coffee-ground” emesis); or melena (blood in the stool)
- **PE:** Usually normal but may reveal epigastric tenderness and stool guaiac

- **Risks:** Acute perforation (rigid abdomen, rebound tenderness, and/or guarding)

Diagnosis

- **Most accurate test:** Upper endoscopy with biopsy is the most accurate test. It can also be used to test for *H pylori* infection and to rule out active bleeding or gastric adenocarcinoma (10% of gastric ulcers without perforation).
- *H pylori* testing. See Table 2.6-6.
- If perforation is suspected, perform upright CXR (see Fig. 2.6-17) to evaluate air under the diaphragm or CT scan of the abdomen.

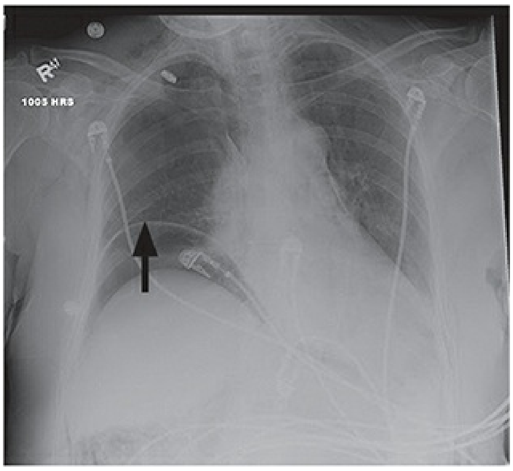


FIGURE 2.6-17. **Pneumoperitoneum.** Upright chest x-ray (CXR) reveals free air under the diaphragm. (Reproduced with permission from USMLE-Rx.com.)

- In recurrent or refractory cases, serum gastrin levels can screen for Zollinger-Ellison syndrome.

Treatment

Acute management:

- **If perforation is suspected:** An upright x-ray of the abdomen (initial test) to rule out free air under the diaphragm. CT (definitive test) if x-ray of the abdomen shows no perforation but there is high clinical suspicion. Surgery if perforation is confirmed on CT.
- **Ruling out active bleeding:** Serial hemoglobin/hematocrits (initially), rectal vault exam, nasogastric (NG) suction. Monitoring blood pressure (BP) and treating with IV hydration, blood transfusion, and IV PPIs. An urgent EGD (definitive) to control suspected bleeding. If bleeding not controlled with EGD, may need surgery or coiling embolization to gastroduodenal artery.

KEY FACT

Anterior duodenal ulcers have a tendency to perforate, whereas posterior duodenal ulcers have a tendency to cause bleeding from erosion through the gastroduodenal artery.

Long-term management:

- **Medical therapy goals:** Protecting the mucosa, ↓ acid production, and eradicating *H pylori* infection
  - Mild disease: Treatment with antacids, PPIs, or H_2-blockers

  - *H pylori* infection: Triple therapy (omeprazole, clarithromycin, and amoxicillin)
  - Discontinuation of exacerbating agents (alcohol, tobacco)
- **Endoscopy with targeted biopsy:** Indicated in patients with symptoms refractory to medical therapy to rule out gastric cancer
- **Surgical therapy (eg, parietal cell vagotomy):** Severe cases refractory to medical therapy

KEY FACT

Uncomplicated, NSAID-induced ulcers are treated with PPIs. However, providers must routinely reassess for the need for NSAIDs and may consider switching to a COX-2 selective NSAID.

Complications

Hemorrhage (most likely from posterior ulcers that erode into the gastroduodenal artery), gastric outlet obstruction (presenting with succussion splash), perforation, and intractable pain.

ZOLLINGER-ELLISON SYNDROME

Rare condition characterized by gastrin-secreting neuroendocrine tumors in the duodenum and/or pancreas, leading to high serum gastrin and large, recurrent or intractable ulcers in the duodenum or jejunum.

- ***Hx/PE:*** Recurrent, gnawing, burning abdominal pain; diarrhea; nausea; vomiting; fatigue; weakness; weight loss; and GI bleeding.
- ***Dx:*** Diagnosis of Zollinger-Ellison syndrome dependent on (1) fasting serum gastrin levels >1000 pg/mL and (2) increase in gastrin levels with the administration of secretin; in addition, pH <2.
  - CT indicated to characterize and stage disease
  - Nuclear octreotide scan to facilitate localization of gastrinomas
- ***Tx:*** Moderate- to high-dose PPIs to control symptoms. Surgical resection of the gastrinoma if not metastatic. Somatostatin analogs have also been shown to be effective for symptom control.

KEY FACT

Zollinger-Ellison syndrome:

- Hypercalcemia from hyperparathyroidism
- Epigastric pain (peptic ulcer)
- Diarrhea (caused by mucosal damage and pancreatic enzyme inactivation)

GASTROPARESIS

Common cause of early satiety associated with delayed gastric emptying. Primarily caused by diabetes; other causes: idiopathy, viral infection, medication induction, and postsurgery status.

History/PE

Patients typically have a long-term history of diabetes. Those who are insulin dependent experience nausea, vomiting, early satiety, and postprandial hypoglycemia due to delayed glucose absorption.

Diagnosis

- MRI or CT may help exclude other etiologies.
- Delayed gastric emptying on nuclear scan is diagnostic.
- Fluoroscopic upper GI evaluation can help rule out obstruction.
- An updated hemoglobin A1c (HbA1c) can assess glycemic control.

Treatment

First-line treatments are hydration and diet modifications. Glycemic control is key. Pharmacologic treatments include prokinetics such as metoclopramide and macrolides. Antiemetics relieve nausea. Patients should avoid pramlintide and glucagon-like peptide-1 (GLP1) agonists, which may worsen gastric emptying.

MÉNÉTRIER DISEASE

Characterized by large gastric folds due to hyperplasia of gastric mucosa and reduced gastric acid secretion.

History/PE

Typically seen in adult males and presents with progressive weight loss, vomiting, epigastric pain, and peripheral edema.

Diagnosis

Large gastric folds revealed on endoscopy, but diagnosis made via gastric biopsy. Laboratory evaluation may reveal hypobilirubinemia and anemia.

Treatment

No definitive treatment available. Management is typically supportive and entails diet modification (ie, high protein) and use of PPIs if associated bleeding is present. Patients require yearly endoscopy to screen for associated carcinoma.

GASTRIC BEZOAR

- Gastric bezoars are foreign bodies made up of ingested material most commonly found in the stomach.
- Their composition may include vegetable matter (phytobezoars), hair (trichobezoars, seen in patients with trichotillomania), and/or medications.

History/PE

- Patients may be asymptomatic initially, but they may insidiously develop symptoms such as abdominal pain, nausea, vomiting, early satiety, anorexia, and weight loss.
- Rare complications include gastric/small bowel obstruction (SBO), intussusception or perforation, peritonitis, protein-losing enteropathy, steatorrhea, obstructive jaundice,

pancreatitis, appendicitis, constipation, and pneumatosis intestinalis.
- Physical examination may show abdominal mass (occasionally) or alopecia (trichobezoars).

Diagnosis

- Gastric bezoars are generally found incidentally on imaging such as abdominal x-ray, barium swallow, abdominal ultrasound, or CT.
- Definitive diagnosis occurs with upper GI endoscopy.

Treatment

- Treatment options include chemical dissolution (based on composition of bezoar) for mildly symptomatic bezoars.
- Endoscopic removal may be considered in more severe cases.
- Metoclopramide or other promotility drugs may be used as an adjuvant treatment with chemical or endoscopic therapy.
- Surgery is considered if other treatment options fail.
- Good hydration, dietary modification, chewing or psychiatric evaluation may be required to prevent recurrence.

BARIATRIC SURGERY

Generally speaking, bariatric surgery is a procedure performed to promote weight loss. These surgeries promote weight loss through limiting caloric intake (by decreasing the size of the stomach) and through decreasing the ability of the body to absorb nutrients (by shortening the length of the bowel). There are several procedures with which to achieve these goals, a few of the more common ones are discussed here.

Indications for Bariatric Surgery

Most bariatric surgeons encourage/require patients to utilize lifestyle changes before surgery in addition to satisfying the following criteria to show true commitment to weight loss:

1. Body mass index (BMI) ≥40 kg/m^2
2. BMI 35 to 39.9 kg/m^2 with at least one serious comorbidity (type 2 diabetes mellitus [DM], obstructive sleep apnea [OSA], Pickwickian syndrome, hypertension, hyperlipidemia, others)
3. BMI 30 to 34.9 kg/m^2 with uncontrolled type 2 DM or metabolic syndrome

Types of Bariatric Surgery

1. **Roux-n-Y gastric bypass:** Division of the proximal stomach from the distal stomach and division of the jejunum. The proximal portion of the stomach is then surgically anastomosed to the distal limb (the “Roux limb”) of the jejunum (gastrojejunal anastomosis). The proximal portion of the jejunum is surgically anastomosed to a more distal portion of the jejunum (jejunojejunal anastomosis), which was previously anastomosed to the proximal stomach.
2. **Sleeve gastrectomy:** Removal of one-third to two-thirds of the stomach surgically.
3. **Adjustable gastric band:** Placement of a silicone band around the stomach with an attached under-skin port. The port is able to be accessed for injections of saline to inflate/deflate the balloon, allowing adjustments to the band, if necessary.

Common complications: Dependent on the specific type of bariatric surgery. Common complications include acid reflux, cholelithiasis, malnutrition, leak at the surgical site, and dumping syndrome.

Dumping Syndrome

Caused by rapid emptying of food from the stomach into the small bowel. The hyperosmolar content osmotically pulls fluids from the plasma into the bowel, causing hypotension and reflex activation of the sympathetic nervous system.

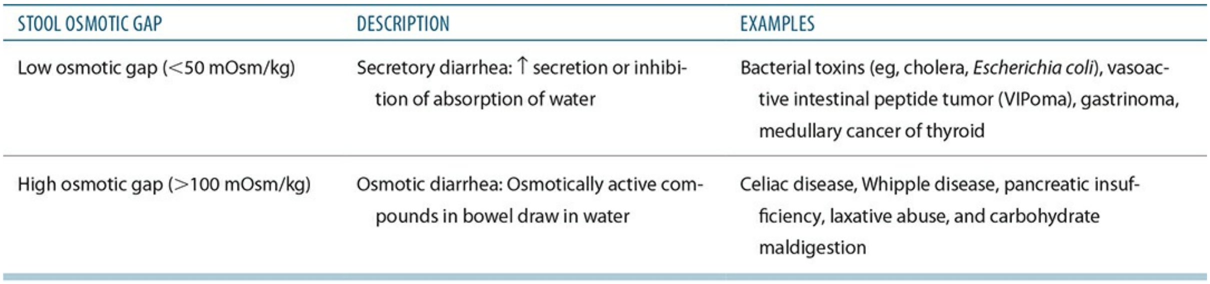
- ***Hx/PE:*** Colicky abdominal pain, diarrhea, tachycardia, and nausea
- ***Dx:*** Made clinically
- ***Tx:*** Avoiding simple sugars; increasing dietary fiber/protein; eating small, frequent meals; separating consumption of solid from liquid foods by ~30 minutes
- ***Px:*** Resolves on its own in 7 to 12 weeks

DISORDERS OF THE SMALL BOWEL

DIARRHEA

- The most common mechanisms are malabsorption/osmotic, secretory, inflammatory/infectious, and ↑ motility (see Tables 2.6-7 and 2.6-8).

TABLE 2.6-7. Types of Stool Osmotic Gap



STOOL OSMOTIC GAP	DESCRIPTION	EXAMPLES
Low osmotic gap (<50 mOsm/kg)	Secretory diarrhea: ↑ secretion or inhibition of absorption of water	Bacterial toxins (eg, cholera, *Escherichia coli*), vasoactive intestinal peptide tumor (VIPoma), gastrinoma, medullary cancer of thyroid
High osmotic gap (>100 mOsm/kg)	Osmotic diarrhea: Osmotically active compounds in bowel draw in water	Celiac disease, Whipple disease, pancreatic insufficiency, laxative abuse, and carbohydrate maldigestion

TABLE 2.6-8. Causes of Infectious Diarrhea

INFECTIOUS AGENT	HISTORY	EXAM AND TEST RESULTS (NOTE: ALL HAVE FECAL RBCs AND WBCs)	COMMENTS	TREATMENT
Campylobacter jejuni	The most common etiology of bacterial diarrhea Caused by ingestion of contaminated food or water Affects young children and young adults; generally lasts 7–10 days	Frequently presents with bloody diarrhea	Rule out appendicitis and IBD	Supportive treatment first, then fluoroquinolones (eg, ciprofloxacin) or azithromycin
Clostridioides difficile	Associated with recent treatment with antibiotics (penicillins, quinolones, clindamycin) Affects hospitalized adult patients Important to watch for toxic megacolon (on x-ray of the abdomen)	Presents with fever, abdominal pain, and possible systemic toxicity	Most commonly causes colitis, but can involve the small bowel Identify *C difficile* toxin in the stool Sigmoidoscopy shows pseudomembranes	Cessation of the inciting antibiotic Nonsevere: PO fidaxomicin or vancomycin Severe (first episode): PO fidaxomicin > PO vancomycin Recurrent (first episode): PO fidaxomicin is preferred over PO vancomycin Recurrent (second or subsequent recurrence): PO fidaxomicin > PO vancomycin Fulminant without ileus: PO vancomycin + parenteral metronidazole Fulminant with ileus: PO or rectal vancomycin + parenteral metronidazole
Echinococcus granulosus	Contracted from close contact with dogs, definitive host for tapeworm Causes simple liver cysts	"Eggshell calcification" on CT scan Usually found incidentally, but may cause mild right upper quadrant (RUQ) pain caused by compression of other structures	Cyst aspiration may cause cyst rupture and anaphylactic shock	Surgical resection and albendazole

INFECTIOUS AGENT	HISTORY	EXAM AND TEST RESULTS (NOTE: ALL HAVE FECAL RBCs AND WBCs)	COMMENTS	TREATMENT
Entamoeba histolytica	Caused by ingestion of contaminated food or water May relate to possible patient history of traveling in developing countries Incubation period lasting up to 3 months	Presents with severe abdominal pain and fever Endoscopy shows "flask-shaped" ulcers	Chronic amebic colitis mimics IBD	Steroids can lead to fatal perforation Treat with metronidazole
Escherichia coli	Caused by ingestion of contaminated food (raw meat) Affects children and older adults Generally lasts 5-10 days	Presents with severe abdominal pain, low-grade fever, and vomiting	It is important to rule out GI bleeding and ischemic colitis Hemolytic uremic syndrome (HUS) is a potential complication (especially for serotype O157:H7), primarily in children	Antibiotic or antidiarrheal therapy to be avoided because they ↑ HUS risk
Salmonella spp.	Classically caused by ingestion of contaminated poultry or eggs, but many other foods may be contaminated Affects young children and the elderly; generally lasts 2-5 days	Presents with a prodromal headache, fever, myalgia, and abdominal pain	Sepsis is a concern, as 5%–10% of patients become bacteremic Sickle cell patients are susceptible to invasive disease leading to osteomyelitis	First fluids; at-risk patients (eg, sickle cell patients) or those with bacteremia treated with oral quinolone or trimethoprim-sulfamethoxazole (TMP-SMX)
Shigella spp.	Extremely contagious; transmitted between people by the fecal-oral route Affects young children and institutionalized patients	Presents with high fever, abdominal pain, and cramping	*Shigella* spp. May lead to severe dehydration It can also cause febrile seizures in the very young Diarrhea may initially be watery and progress to become bloody/mucoid	A fluoroquinolone + azithromycin + third generation cephalosporin or TMP-SMX + ampicillin to prevent person-to-person spread
Taenia solium	Pork tapeworm Acquired by ingestion of undercooked pork	Presents with signs of elevated intracranial pressure (headaches, vomiting, seizures, visual changes)	*T solium* is diagnosed via CT or MRI showing several cysts with edema	Treatment with albendazole and with symptomatic management of CNS symptoms
Trichinella spiralis	Acquired by ingestion of undercooked meat (primarily pork) in developing countries (especially Mexico and Thailand)	Classic triad of myositis, periorbital edema, and eosinophilia Possibility for migrating larvae to cause vasculitis, leading to splinter hemorrhages	Multiorgan involvement is possible	Albendazole (or mebendazole); corticosteroids in severe cases

- **Stool electrolytes:** Primarily sodium and potassium (normal stool osmotic gap is 50–100 mOsm/kg). Stool osmotic gap = 290 – 2 × (stool Na + stool K).

KEY FACT

Cryptosporidium and *Isospora* are associated with chronic diarrhea in patients with HIV/AIDS.

History/PE

- **Acute diarrhea:** Acute onset with a duration of <2 weeks; usually infectious and self-limited
  - Possibility for multiple pathogens to be responsible (see Table 2.6-8)
  - Common causes of pediatric diarrhea—rotavirus, Norwalk virus, and enterovirus infection
- **Chronic diarrhea:** Often insidious onset with a duration of >4 weeks
  - **Secretory:** Carcinoid tumors, vasoactive intestinal peptide (VIP)omas
  - **Malabsorption/maldigestive/osmotic:** Bacterial overgrowth, pancreatic insufficiency, mucosal damage, lactose intolerance, celiac disease, laxative abuse (presents with dark-brown colonic discoloration), postsurgical short bowel syndrome
  - **Inflammatory/infectious:** IBD, giardiasis, amoebic dysentery
  - **Increased motility:** Irritable bowel syndrome (IBS)

KEY FACT

Organisms that cause bloody diarrhea include *Salmonella*, *Shigella*, enterohemorrhagic *Escherichia coli* (EHEC), and *Campylobacter*.

Diagnosis

- **Acute diarrhea:** No further studies indicated unless the patient has a high fever, bloody diarrhea, or diarrhea lasting >4 to 5 days.
- **Chronic diarrhea:** History/physical examination to narrow the differential diagnosis. Additional studies include the following:
  - **Secretory:** Carcinoid tumors, VIPomas, bile acid diarrhea (Ileal malabsoprtion of bile acids [due to ileal resection, ileal Crohn’s disease] results in excess bile acids in colon. Bile acids increase colonic secretion and motility)
  - **Stool analysis:** Leukocytes, culture, *Clostridioides difficile* toxin, and ova and parasite exam (O&P)

KEY FACT

Organisms that cause watery diarrhea include *Vibrio cholerae*, rotavirus, enteropathogenic *E coli* (ETEC), *Cryptosporidium*, *Giardia*, and norovirus.

Treatment

- **Acute diarrhea:** Oral rehydration key. Antibiotics are not indicated (except in *C difficile* infection or in the epidemic setting) because they do not shorten the course of illness.
- **Chronic diarrhea:** Treatment specific to etiology.

KEY FACT

Diarrhea after ingestion of raw eggs or dairy: think *Salmonella*.

MALABSORPTION/MALDIGESTION

- Inability to absorb macronutrients and/or micronutrients. Presents with chronic diarrhea with weight loss, growth failure, and macronutrient and/or micronutrient deficiencies.
- **Celiac disease:** Characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia in response to dietary gluten exposure. Celiac disease is associated with extraintestinal manifestations, including dermatitis herpetiformis (see Fig. 2.6-18) and autoimmune diseases of thyroid gland, liver, and type 1 diabetes.

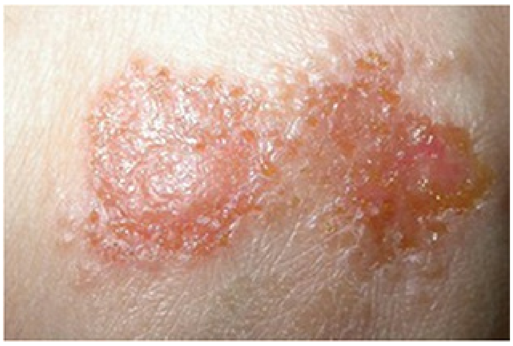


FIGURE 2.6-18. **Dermatitis herpetiformis.** Grouped, papulovesicular, pruritic skin lesions are shown. Lesions tend to be symmetrically located on the extensor surfaces of the elbows, knees, buttocks, and posterior scalp and are associated with celiac disease. (Reproduced with permission from Caproni M et al. Celiac disease and dermatologic manifestations: many skin clues to unfold gluten-sensitive enteropathy. *Gastroenterol Res Pract.* 2012;2012:952753.)

Diagnosis

- Serologic testing is crucial for screening and diagnosis and includes anti–tissue transglutaminase-IgA (TTG-IgA) and endomysial IgA antibody testing.
- Histologic analysis of duodenal biopsies is gold standard for diagnosis and grading based on Marsch classification.
- Celiac disease has a strong genetic component, but testing for HLA-DQ2/DQ8 has limited role in diagnosis.

Management

- Lifelong adherence to gluten-free diet is the cornerstone of treatment and results in symptom resolution and mucosal healing.
- Concomitant testing for micronutrient deficiencies (iron, folic acid, vitamins D, B_{12}) should be undertaken and repleted as needed.
- Close monitoring for other autoimmune diseases (thyroid, liver, type 1 diabetes) and osteoporosis should be done.

Other etiologies of malabsorption:

- **Mucosal abnormalities:** Whipple disease (also presents with arthritis, lymphadenopathy, cardiac issues, periodic acid–Schiff [PAS]–positive granules in lamina propria on biopsy), tropical sprue (chronic diarrhea and nutritional malabsorption [vitamin B_{12} and vitamin B_9] and living >1 month in an endemic area)
- **Bile salt deficiency:** Ileal disease in Crohn disease or small bowel resections (>100 cm of terminal ileum), bacterial overgrowth
- **Short bowel syndrome:** Caused by resection of small bowel; results in malabsorption of both micronutrients and macronutrients; amount of bowel resection weakly correlated to likelihood/degree of symptoms
- **Small intestinal bacterial overgrowth (SIBO):** Bacterial overgrowth due to various

causes, resulting in bloating or chronic watery diarrhea. Underlying etiologies include abnormal motility, abnormal anatomy (eg, after abdominal surgery, GI cancer), metabolic and systemic disorders (eg, diabetes), and immune disorders (eg, IgA deficiency)

- ***Hx/PE:*** Presents with pale, foul-smelling, bulky stools (steatorrhea or fat maldigestion) associated with abdominal pain, flatus, bloating, weight loss, nutritional deficiencies, and fatigue.

KEY FACT

The initial tests specific for celiac disease are IgA anti-transglutaminase antibody or antiendomysial antibody. The gold standard is intestinal biopsy, which will show increased intraepi-thelial lymphocytes (>25 per 100 enterocytes), crypt hyperplasia, and villous atrophy.

- ***Dx:*** Multiple laboratory tests based on clinical suspicion. Biopsy is definitive.
- ***Tx:*** Etiology dependent. In severe cases, patients may require total parenteral nutrition (TPN), immunosuppressants, and anti-inflammatory medications. Dapsone can be used for dermatitis herpetiformis.

CARBOHYDRATE MALDIGESTION

Lactase Deficiency

Can be primary (autosomal recessive) or secondary (acquired conditions that affect structural or functional integrity of small bowel).

- Common among populations of African, Asian, and Native American descent, also transiently after an acute episode of gastroenteritis.
- ***Hx/PE:*** Presents with abdominal bloating, flatulence, cramping, and watery diarrhea following dairy ingestion.
- ***Dx:*** Often treated empirically with lactose-free diet. Hydrogen breath test reveals ↑ hydrogen following the ingestion of lactose.
- ***Tx:*** Avoidance of dairy products; oral lactase enzyme replacement.

Other Forms of Carbohydrate Maldigestion

- Sucrase-isomaltase deficiency: Rare homozygous recessive disorder with sucrose maldigestion.
- Maltase-glucoamylase deficiency.
- Fructose intolerance: Can be hereditary (presents in infancy) or dietary (later in life). No standardized diagnostic tests are available, but fructose breath test can be suggestive. Treatment involves restricting fructose in diet.

KEY FACT

Patients with carcinoid syndrome also develop niacin/vitamin B_3 deficiency (pellagra) because tryptophan is metabolized into serotonin.

CARCINOID SYNDROME

Carcinoid syndrome is caused by metastasis of carcinoid tumors, which most commonly arise from the ileum and appendix and produce serotonin. Prior to metastasis, most secreted hormones undergo first-pass metabolism by the liver and do not cause systemic symptoms.

- ***Hx/PE:*** Cutaneous flushing, watery diarrhea, abdominal cramps, wheezing, and right-sided cardiac valvular lesions are the most common manifestations.
- ***Dx:*** High urine levels (elevated 24-hour urinary excretion) of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) (best initial test) are diagnostic. CT and In-111 octreotide scans are used to localize the tumor.
- ***Tx:*** Treatment includes octreotide for symptomatic patients and surgery in resectable disease.

MNEMONIC

The classic presentation of pellagra (deficiency in niacin/vitamin B_3) is the **4 Ds: D**iarrhea, **D**ementia, **D**ermatitis, and **D**eath.

SMALL BOWEL OBSTRUCTION

- Partial or complete blockage of passage of bowel contents through the small bowel.
- **Etiologies:** Adhesions (60% of cases), hernias (10%–20%), neoplasms (10%–20%), intussusception, gallstone ileus, stricture, and volvulus
- **Partial SBO:** Continued passage of flatus, but no stool
- **Complete SBO:** No passage of flatus or stool (obstipation)

KEY FACT

In the United States, the leading cause of SBO in children is hernia. The leading cause of SBO in adults is adhesions.

History/PE

- **History:** Crampy abdominal pain at 4- to 5-minute intervals. Vomiting typically follows the pain.
- **Abdominal exam:** Distention, tenderness, prior surgical scars, or hernias; hyperactive bowel sounds (high-pitched tinkles and peristaltic rushes).
- **Complications:** Ischemic necrosis and bowel rupture with prolonged or complete obstruction. Patients present with peritonitis manifested by fever, hypotension, rebound tenderness, and tachycardia.

Diagnosis

- **Best initial test:** Abdominal x-ray demonstrates a stepladder pattern of dilated small bowel loops, air-fluid levels (see Fig. 2.6-19), and a paucity of gas in the colon.

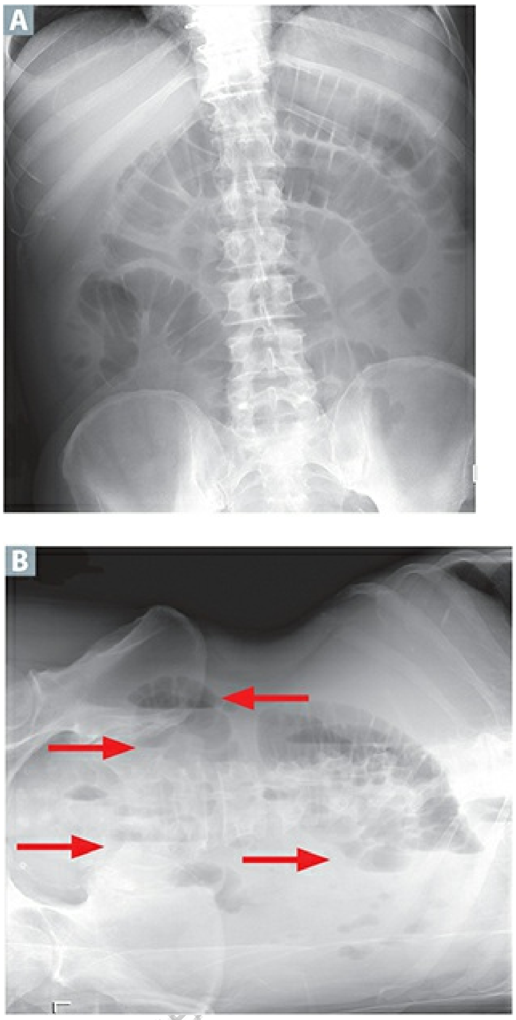


FIGURE 2.6-19. **Small bowel obstruction. (A)** Supine x-ray of the abdomen shows dilated air-filled small bowel loops with relatively little gas in the colon. **(B)** Left lateral decubitus x-ray on the same patient demonstrates multiple air-fluid levels *(arrows)* at different levels. These are typical plain film findings of complete SBO. (Reproduced with permission from Doherty GM. *Current Diagnosis & Treatment: Surgery,* 13th ed. New York, NY: McGraw-Hill; 2010.)

- **Most accurate test:** CT scan of the abdomen further characterizes obstruction and evaluates for etiology.
- Complete blood cell count (CBC) may demonstrate leukocytosis if there is ischemia or necrosis of bowel.
- Lab tests often reveal dehydration. Lactic acidosis is a prognostic sign, as it suggests necrotic bowel.

Treatment

- **Best initial treatment:** Fluid resuscitation.
- **Partial obstruction:** Supportive care sufficient. It should include NPO status, NG suction, IV hydration, correction of electrolyte abnormalities, Foley catheterization to monitor fluid status, and pain management. Patient should avoid opioids and anticholinergics (slow GI motility).
- **Complete obstruction:** Exploratory laparotomy indicated if there is presence of bowel necrosis, perforation, ischemia, or a surgically correctable cause of complete SBO. Otherwise, nonoperative management can be utilized for a period of time if the patient is

clinically stable.

KEY FACT

Gallstone ileus is a form of SBO that occurs when a gallstone lodges at the ileocecal valve after passing through a cholecystoenteric fistula.

ILEUS

Loss of peristalsis without structural obstruction.

Risk Factors

Recent surgery/GI procedures, severe medical illness, immobility, hypokalemia or other electrolyte imbalances, hypothyroidism, DM, and medications that slow GI motility (eg, anticholinergics, opioids).

History/PE

- Diffuse, constant abdominal discomfort; nausea and vomiting; an absence of flatus or bowel movements.
- Diffuse tenderness, abdominal distention, and ↓ or absent bowel sounds. A rectal exam is required to rule out fecal impaction in older adult patients.

Q

A 53-year-old woman with a history of carcinoid tumor of the appendix (status post-resection) presents to a local clinic with symmetric, dry, hyperpigmented skin lesions and persistent diarrhea. Her husband expresses concern that the patient does not seem to be herself anymore; he reports that she has been irritable, confused, and forgetful. What is the most likely diagnosis?

KEY FACT

In ileus, there is air present throughout the small and large bowel on x-ray of the abdomen.

Diagnosis

- Must consider clinical history in diagnosis.
- **Best initial test:** Abdominal film showing distended loops of small and large bowel, with air seen throughout the colon and rectum (SBO has no air distal to the obstruction).
- **Most accurate test:** CT scan of the abdomen.

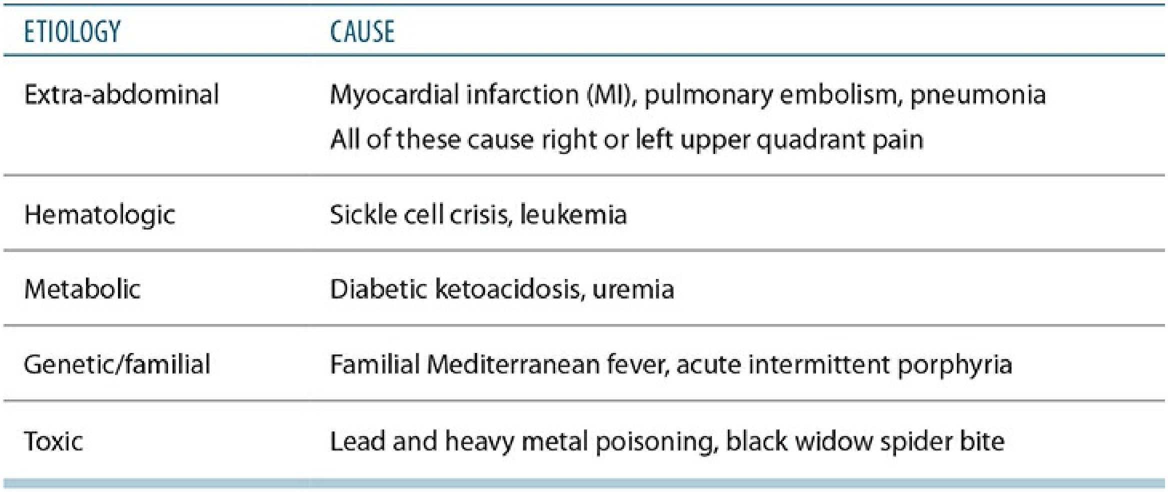
Treatment

- ↓ or discontinue the use of narcotics and any other drugs that reduce bowel motility.
- **Bowel rest:** Temporarily ↓ or discontinue oral feeds.
- **Bowel decompression:** Initiate low, intermittent NG suctions and parental feeds.
- **Supportive care:** Replete electrolytes as needed; hydrate with IV fluids.

ACUTE ABDOMEN

Any condition that presents with new-onset, severe abdominal pain and tenderness. These patients usually require surgery, but many nonsurgical mimics exist. A physician should always consider a gynecologic etiology in females and nonsurgical causes of acute abdomen (see Table 2.6-9) in all patients.

TABLE 2.6-9. Nonsurgical Causes of Acute Abdomen



ETIOLOGY	CAUSE
Extra-abdominal	Myocardial infarction (MI), pulmonary embolism, pneumonia All of these cause right or left upper quadrant pain
Hematologic	Sickle cell crisis, leukemia
Metabolic	Diabetic ketoacidosis, uremia
Genetic/familial	Familial Mediterranean fever, acute intermittent porphyria
Toxic	Lead and heavy metal poisoning, black widow spider bite

History/PE

In general, four pathologies contribute to acute abdomen and present with characteristic symptoms. Considering these mechanisms along with location and associated history/physical examination findings may help delineate the diagnosis.

The four pathologies are perforation/rupture, obstruction, inflammation, and ischemia.

- **Perforation or rupture:** Sudden onset of diffuse, excruciating pain. Patients will lie still to minimize pain. Peritoneal signs are prominent.
  - **Esophageal perforation (Boerhaave syndrome):** Has been associated with recurrent vomiting/hematemesis, but up to 45% of patients have no history of emesis. Esophageal perforation commonly presents with retrosternal and epigastric pain.
  - **Other GI perforation:** Associated with PUD, cancer, diverticulitis, and IBD.
  - **Ruptured abdominal aortic aneurysm (AAA):** Most common in male smokers >65 years of age. Patient may describe periumbilical pain that radiates to the back. Abdominal exam may reveal pulsatile mass.

A

Pellagra, a deficiency of vitamin B_3 (niacin), secondary to a recurrent carcinoid tumor. Carcinoid tumors produce serotonin, which is a derivative of tryptophan. However, tryptophan is also the precursor of niacin. In patients with carcinoid tumors, the tumor can be so active that most tryptophan is used for serotonin production, resulting in niacin deficiency.

  - **Ruptured ectopic pregnancy/ovarian cyst:** Presents with first-trimester bleeding, abdominal pain, and hypovolemic shock. Abdominal pain is usually localized to the pelvis, but specific location and quality of pain are variable.

KEY FACT

β-Human chorionic gonadotropin (β-Hcg) is a vital sign in women with acute abdomen. ⊕ β-Hcg in the setting of shock is a ruptured ectopic pregnancy until proven otherwise.

- **Obstruction:** Sudden onset of severe, colicky, intermittent pain. Patients cannot sit still. Peritoneal signs are usually absent.
  - **SBO:** Most commonly from adhesions years after abdominal surgery, incarcerated hernias, or in patients with IBD or cancer. Patient may complain of obstipation (failure to pass stool or gas). Bowel sounds are high-pitched early in the disease process.
  - **Volvulus:** Abdominal pain with insidious onset that is continuous, with intermittent exacerbations associated with peristalsis. Patients also complain of nausea, distention, and obstipation. Immediate surgery is pursued in the presence of peritonitis or perforation. Otherwise, endoscopic detorsion may be used for management of sigmoid volvulus. Cecal volvulus is mostly treated surgically.
  - **Ureteric/biliary obstruction:** Nephrolithiasis causing colicky pain that usually radiates to the groin and may cause hematuria/pyuria. This condition may also cause costovertebral angle tenderness (CVAT). Biliary colic is most common in multiparous, overweight women (**f**emale, **f**orty, **f**ertile, and **f**at). Fatty meals exacerbate pain. There are no signs of peritoneal irritation.

KEY FACT

Adhesions are the most common cause of small bowel obstruction in patients with a history of abdominal surgeries.

- **Inflammation:** Gradual onset (over 10–12 hours) of constant, poorly localized pain that later localizes to problem area. Patients lie still to minimize pain. Peritoneal signs are prominent.
  - **Appendicitis:** Detailed later.
  - **Cholecystitis:** Same demographics as biliary colic. Pain is constant. Peritoneal irritation is evident. Murphy sign causes pain on inspiration.
  - **Diverticulitis:** Prominent left lower quadrant (LLQ) pain, change in bowel habits, and ± nausea/vomiting. Palpation or rectal exam may reveal mass (abscess).
  - **Pelvic inflammatory disease (PID):** Associated with history of sexually transmitted diseases or occurring in young females with unsafe sexual practices. Pelvic exam elicits cervical motion tenderness and adnexal tenderness.
- **Ischemia:** Variable presentation, dependent on specific etiology.
  - **Acute mesenteric ischemia:** Sudden onset of pain and hematochezia in a patient with history of atrial fibrillation.
  - **Ischemic colitis:** Postprandial abdominal pain ± hematochezia/melena in a patient with significant atherosclerotic disease (prior myocardial infarction [MI]/stroke, peripheral artery disease).
  - **Strangulated hernia:** Irreducible bulge in abdominal wall.
  - **Ovarian torsion:** Sudden onset of adnexal pain ± nausea/vomiting. Character of pain is variable. Palpation usually reveals a mass. Condition has a high index of suspicion in females since clinical presentation is variable.

KEY FACT

Acute abdominal pain with blood per rectum is acute mesenteric ischemia until proven otherwise. Classically, an older adult patient with a history of atrial fibrillation or recent AAA repair presents with these findings.

Diagnosis

- **To rule out OB/GYN causes in women:** Urine β-human chorionic gonadotropin (β-Hcg) for ectopic pregnancy; pelvic ultrasound for ovarian torsion, ruptured cyst, or fibroids; pelvic exam ± swab for PID
- **To rule out extra-abdominal mimics in patients with upper abdominal pain:** Troponins and ECG for MI, D-dimer/CT angiogram for pulmonary embolism, CXR for pneumonia
- **To rule out nonsurgical abdominal causes, if appropriate:** Amylase/lipase in patient consistent with pancreatitis (nausea/vomiting, epigastric pain, hunched over), CT abdomen without contrast in patient consistent with kidney stones/pyelonephritis (hematuria, flank pain, radiation to groin), paracentesis for patient consistent with systolic blood pressure (ascites, fever)
- **Additional diagnostic tests to rule in surgical diagnoses:**
  - **X-ray of the abdomen:** Perforation (see Fig. 2.6-20), SBO, volvulus

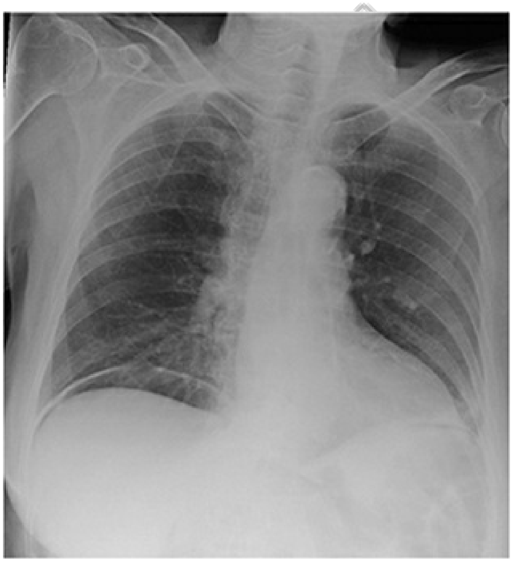


FIGURE 2.6-20. **Pneumoperitoneum.** Free gas under the right and left hemi-diaphragms visible in erect CXR. This may occur due to small bowel perforation. (Reproduced with permission from Buckle C, Holdridge C, Xu T, et al. Acute abdominal pain and radiological pneumoperitoneum: always an Indication for Laparotomy? *J Clin Med Res* 2013;5:2. doi: 10.4021/jocmr929w.)

  - **CT with contrast:** Appendicitis, diverticulitis, IBD, abscess, cancer, AAA
  - **Right upper quadrant (RUQ) ultrasound:** Cholecystitis, biliary colic, choledocholithiasis

Management

A detailed approach to management is beyond the scope of this section, but general concepts are as follows:

- In the presence of peritoneal signs or shock: Exploratory laparotomy.

- All unstable patients and those with suspected potential hemorrhage: Blood typing, cross-matching and transfusion as needed.
- Patients with perforation or signs of sepsis: Broad-spectrum antibiotics. Treatment with these antibiotics is also indicated for patients with suspected infectious processes (cholecystitis, diverticulitis, pyelonephritis).
- Stable patients: Expectant management, possibly including NPO status, NG tube placement (for decompression of bowel in the setting of obstruction or acute pancreatitis), IV fluids, placement of a Foley catheter (to monitor urine output and fluid status), and vital sign monitoring with serial abdominal exams and serial labs.

DUODENAL HEMATOMA

Duodenal injuries are rare and involve the second part of the duodenum most commonly. Duodenal injuries are often accompanied by injuries to surrounding structures in the retroperitoneal region. Initial presentation can be nonspecific, and suspicion should arise in cases with direct blow or impact to the mid-abdomen.

Etiology

- In children, may result from a blunt trauma through bicycle handlebar or abuse.
- In adults, more often due to penetrating injuries (eg, gun shot, stabbing). Nonpenetrating injuries with duodenal hematoma in adults are typically due to steering wheel injuries.

History/PE

- Typically, signs and symptoms are nonspecific. Patients may have signs and symptoms of GI obstruction such as bilious emesis, with an inability to tolerate oral intake.
- Presentation is often insidious, leading to delayed diagnosis. Some patients develop symptoms 48 hours after injury (due to gradual fluid shift into hyperosmotic hematoma).
- PE: Ecchymosis may be seen in the pattern of injury (crush injury with bicycle handlebar or seat belt sign), abdominal tenderness, peritonitis, or palpable upper abdominal mass.

Diagnosis

- Abdominal CT is the best initial test for duodenal injury in hemodynamically stable patients. Alternatively, upper GI series may be used (shows coiled spring sign or obstruction).
- Patients who are hemodynamically unstable may be diagnosed during explorative laparotomy.
- Pancreatic injury and other associated injuries should be excluded.

Treatment

- For blunt duodenal injuries, nonsurgical management in hemodynamically stable patients is recommended. Patients receive NG suction and TPN. Patients are followed with upper GI series or ultrasound at 5-day to 7-day intervals if signs of obstruction do not abate. Surgery may be considered if conservative management fails.
- For penetrating duodenal injury, conservative management is not recommended, and patients should undergo surgery (duodenal repair, decompression, and other procedures).

MESENTERIC ISCHEMIA

Insufficient blood supply to the small intestine, resulting in ischemia and, potentially, necrosis. See Table 2.6-10 for clues to differentiating between types of ischemia. The most common causes are as follows:

TABLE 2.6-10. Differentiating Types of Mesenteric Ischemia

	ACUTE MESENTERIC ISCHEMIA	ISCHEMIC COLITIS	CHRONIC MESENTERIC ISCHEMIA
Site	Small intestine	Large intestine, watershed zones (splenic flexure and rectosigmoid junction)	Small and large intestine
Etiology	Thromboembolic (atherosclerosis, atrial fibrillation, oral contraceptives) Cholesterol emboli after percutaneous vascular procedures	Transient decrease in perfusion pressure due to decreased cardiac output (eg, dehydration, shock)	Fixed progressive obstruction in blood flow (eg, atherosclerosis of mesenteric vessels)
Symptoms	Sudden-onset severe pain, diarrhea (bloody or nonbloody) Pain "out of proportion" to examination findings	Bloody diarrhea with abdominal pain	Postprandial pain leading to fear of eating and weight loss
Investigations	X-ray: ileus, may show portal venous gas or gas within the walls (pneumatosis intestinalis) CT angiogram—investigational method of choice	X-ray: Thumbprinting of watershed areas of colon	Duplex ultrasonography
Treatment	Supportive measures with fluids; antibiotic therapy followed by surgery/embolectomy	Optimization of cardiac output with fluids, treatment of shock	May require revascularization, either surgical or percutaneous

- **Embolism:** Most commonly originates in the heart. Risk factors include atrial fibrillation and stasis from ↓ ejection fraction.
- **Acute arterial occlusion from thrombosis:** Most commonly occurs in the proximal superior mesenteric artery (SMA). The primary risk factor is atherosclerosis.
- **Other causes:** Nonocclusive arterial disease (atherosclerosis of mesenteric vessels, arteriolar vasospasm), venous thrombosis (caused by hypercoagulable states), or shock state.

History/PE

Presents with severe abdominal pain out of proportion to the examination, nausea, vomiting, diarrhea, bloody stools, prior episodes of abdominal pain after eating ("intestinal angina").

Diagnosis

- **Best initial test:** X-ray or CT scan of the abdomen may reveal bowel wall edema ("thumbprinting") and air within the bowel wall (pneumatosis intestinalis).
- **Most accurate test:** Mesenteric/CT angiography is the gold standard for diagnosis of arterial occlusive disease, but conventional angiography allows for intervention of thrombosis/embolism.

Treatment

- **Best initial treatment:** Volume resuscitation, broad-spectrum antibiotics
- **For acute arterial thrombosis or embolism:** Anticoagulation and either laparotomy or angioplasty

Q

A 65-year-old male smoker is brought to the emergency department for sudden-onset abdominal and back pain. The anxious patient complains of “ripping pain.” Physical examination reveals a large, pulsatile mass behind the umbilicus. BP is 80/50 mm Hg; heart rate 125 beats per minute (bpm). The physician begins crystalloid and blood infusions. What is the most appropriate next step in management?

- **For venous thrombosis:** Anticoagulation
- **Surgery:** Resection of infarcted bowel

Complications

Sepsis/septic shock, multisystem organ failure, death

KEY FACT

Cholesterol embolism may occur after cardiac catheterization, and ischemia of multiple organs may be seen (bowel, kidney, pancreas, lower extremity skin causing livedo reticularis).

ACUTE APPENDICITIS

Obstruction of the appendiceal lumen with subsequent inflammation and infection. Rising intraluminal pressure leads to vascular compromising of the appendix, ischemia, necrosis, and possible perforation. Etiologies include hypertrophied lymphoid tissue (55%–65%), fecalith (35%), foreign body, tumor (eg, carcinoid tumor), and parasites. Incidence peaks in the early teens (most patients 10–30 years of age), and the male-to-female ratio is 2:1.

A

Based on the clinical findings of shock, abdominal pain, and a pulsatile mass, the patient has a ruptured abdominal aortic aneurysm (AAA), which is a surgical emergency. If the patient is stable, ultrasonography or urgent CT are the next best steps and inform intervention; however, immediate laparotomy or endovascular repair should not be delayed in the unstable patient.

History/PE

- Classically presents with dull periumbilical pain lasting 1 to 12 hours with subsequent migration to sharp right lower quadrant (RLQ) pain at McBurney point.
- Can present with nausea, vomiting, anorexia, and low-grade fever.
- Psoas, obturator, and Rovsing signs not sensitive tests, but their presence ↑ the likelihood of appendicitis. Psoas abscess can present similarly to appendicitis, but with a more insidious onset over days. CT can distinguish between the two.
- In perforated appendicitis, possibility of partial pain relief. Peritoneal signs (eg, rebound, guarding, hypotension, ↑ WBC count, fever) will ultimately develop.
- Atypical presentations possible in children, older adults, pregnant patients, and those with retrocecal appendices. These may result in misdiagnosis and ↑ mortality. Atypical or nonspecific features include indigestion, flatulence, diarrhea, bowel irregularity, and

generalized malaise.

KEY FACT

The McBurney point is located one-third of the distance from the anterior superior iliac spine to the umbilicus. It is an important part of a physical examination because this location corresponds to the base of the appendix.

Diagnosis

- Appendicitis is a clinical diagnosis in patients with classic history (described earlier), fever, and leukocytosis.
- Investigation can occur with CT IV contrast (see Fig. 2.6-21) or RLQ ultrasound (preferred in children and pregnant patients).

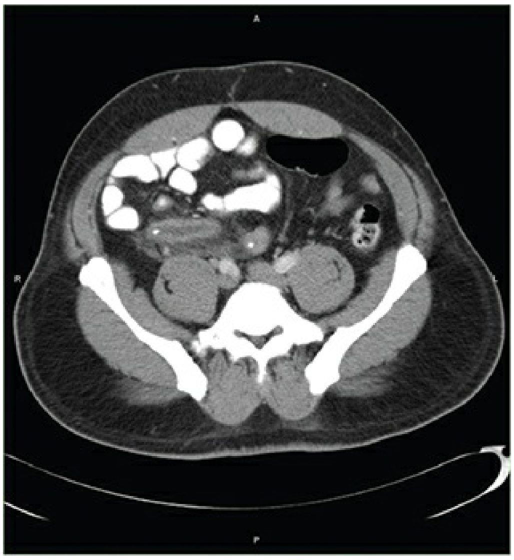


FIGURE 2.6-21. **Acute appendicitis.** Contrast-enhanced CT demonstrating an enlarged, hyperenhancing appendix with an appendicolith visualized in the lumen and periappendiceal fat stranding located anterior to the right posts muscle. (Reproduced with permission from USMLE-Rx.com.)

Treatment

- IV antibiotics with anaerobic and gram ⊖ coverage (eg, cefoxitin or cefazolin plus metronidazole). The patient should be NPO and receive IV hydration, analgesia, and antiemetics.
- **Uncomplicated appendicitis:** Surgery or observation with antibiotics depending on the clinical scenario. If appendicitis not found, complete exploration of the abdomen is performed. There is no need to administer antibiotics postoperatively.
- **Perforation:** Perform immediate open or laparoscopic appendectomy. Administer antibiotics postoperatively until the patient is afebrile with a normalized WBC count. If open approach is used, the incision should be closed by delayed primary closure.
- **Abscess:** Broad-spectrum antibiotics and CT-guided drainage. Interval appendectomy should be performed 6 to 8 weeks after resolution of abscess.

KEY FACT

Surgical incisions can be closed by the following:

- Primary closure (primary intent): Surgical approximation using sutures or staples
- Secondary closure (secondary intent): No approximation, typically packed with gauze, filled in with granulation tissue
- Delayed primary closure (tertiary intent): Similar to primary closure; occurs after several days of observation to permit drainage

DISORDERS OF THE LARGE BOWEL

CLOSTRIDIUM DIFFICILE COLITIS

Traced to spore-forming, toxin-producing, gram-positive anaerobic bacteria that colonize the colon after normal gut flora are disrupted by antibiotics (penicillins, quinolones, cephalosporins, clindamycin). Infection with *C difficile* classically affects adult patients in hospitals and nursing homes, as well as those with significant risk factors (eg, IBD).

History/PE

- It is typically associated with recent antibiotic usage.
- Additional risk factors include age >65 years, recent hospitalization, and use of PPIs.
- Symptoms range from asymptomatic carriage to profuse diarrhea (>3 watery loose stools in 24 hours), fever, abdominal pain, and possible systemic toxicity.
- Infection with *C difficile* most commonly causes colitis, but it can involve the small bowel.

Diagnosis

- *C difficile* toxin can be identified in the stool sample.
- Sigmoidoscopy may be normal or show patchy erythema in mild cases and pseudomembranes in severe cases.

KEY FACT

Lack of history of antibiotic usage does not exclude the possibility of *C. difficile* colitis. Leukocytosis in the absence of diarrhea in a hospitalized patient can be related to *C. difficile* colitis.

Treatment

- Cessation of the inciting antibiotic
- Nonsevere (WBC <15k, Cr <1.5): PO fidaxomicin or PO vancomycin
- First severe (WBC >15k, Cr >1.5): PO fidaxomicin > PO vancomycin
- Recurrent (first, second, and subsequent episodes): PO fidaxomicin > PO vancomycin and consider fecal microbiota transplantation
- Fulminant without ileus: PO vancomycin + parenteral metronidazole
- Fulminant with ileus: PO and rectal vancomycin + parenteral metronidazole

Complications

Toxic megacolon presents with large bowel dilatation (>7 cm diameter in colon or >12 cm in the cecum).

DIVERTICULAR DISEASE

- **Diverticula:** Outpouching of mucosa and submucosa (false diverticula) that herniate through the colonic muscle layers in areas of high intraluminal pressure; most commonly found in the sigmoid colon
- **Diverticulosis:** Presence of many diverticula—most common cause of acute lower GI bleeding in patients >40 years of age. Predominantly left-sided in Western countries. Bleeding usually results from weakened intestinal vasa recta vessels.
- **Diverticulitis** Inflammation following microperforations secondary to fecalith impaction and high luminal pressure.
- **Risk factors:** Diets that worsen constipation (eg, low fiber, red meat, and high-fat content), advanced age (65% occur in those >80 years of age), and connective tissue disorders.

KEY FACT

Diverticulosis is the most common cause of acute lower GI bleeding in patients >40 years of age.

History/PE

- **Diverticulosis (see Fig. 2.6-22):** Often asymptomatic until patients present with sudden, intermittent, painless bleeding, which can cause symptoms of anemia when bleeding is severe. Diverticulosis is associated with chronic constipation, which increases intraluminal pressure of the colon and worsens outpouchings.

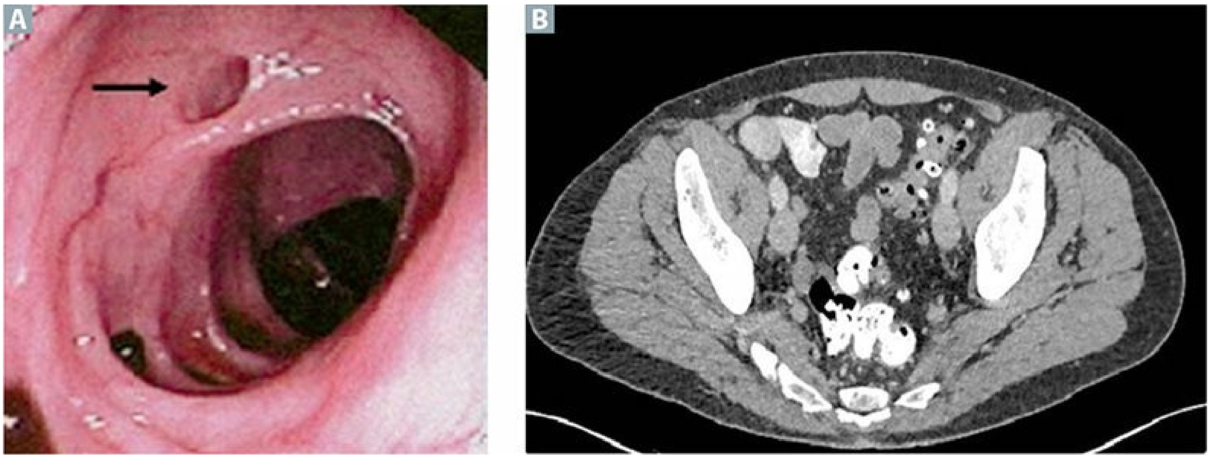


FIGURE 2.6-22. **(A)** An endoscopic view of diverticulosis. **(B)** An axial CT slice visualizing diverticulosis. (Image A adapted with permission from USMLE-Rx.com. Image B adapted with permission from Sartelli M, Moore FA, Ansaloni L, et al. A proposal for a CT driven classification of left colon acute diverticulitis. *World J Emerg Surg.* 2015;10:3. https://doi.org/10.1186/1749-7922-10-3.)

- **Diverticulitis:** LLQ abdominal pain, fever, nausea, and vomiting. Perforation is a serious complication that presents with peritonitis and shock.

Diagnosis

- Clinical history is important to diagnosis.

- CBC may show leukocytosis or anemia.
- **Most accurate test:** Colonoscopy provides definitive diagnosis in diverticular disease; however, sigmoidoscopy/colonoscopy should be avoided in patients with acute diverticulitis because of the risk for perforation.
- In acute diverticulitis, CT scan is the best test for diagnosis; it may reveal inflammation or abscess (see Fig. 2.6-23).

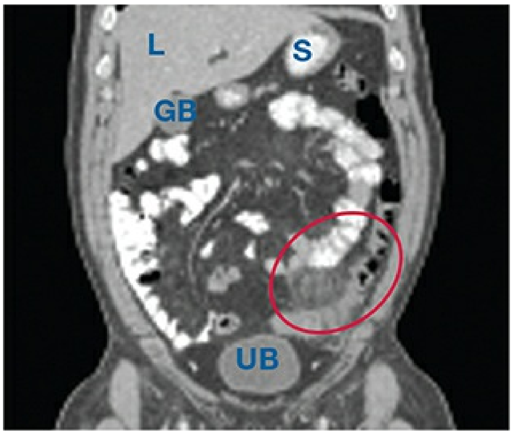


FIGURE 2.6-23. **Acute diverticulitis.** Coronal reconstruction from a contrast-enhanced CT demonstrates sigmoid diverticula with presigmoid inflammatory "fat stranding." The area of abnormality is circled in red. *GB*, gallbladder; *L*, liver; *S*, stomach; *UB*, urinary bladder. (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

Sigmoidoscopy should be avoided when there is clinical and imaging evidence of diverticulitis because of the risk for perforation.

Treatment

- **Uncomplicated diverticulosis:** Routine follow-up is indicated. Patient should receive encouragement to follow a high-fiber diet or take fiber supplements.
- **Diverticular bleeding:** Bleeding usually stops spontaneously; physician should transfuse and hydrate patient as needed. If bleeding does not stop, hemostasis by colonoscopy, angiography with embolization, or surgery is indicated.
- **Diverticulitis:** Treat with bowel rest (NPO), NG tube placement (if severe), and broad-spectrum antibiotics (if complicated, metronidazole and a fluoroquinolone or a second- or third-generation cephalosporin). Uncomplicated, left-sided diverticulitis may initially be treated in the outpatient setting without antibiotics. Colonoscopy can occur after the initial stage.
- **Hospitalization:** If there is evidence of peritonitis or systemic signs of infection.
- **For perforation:** Immediate surgical resection of diseased bowel via a Hartmann procedure with a temporary colostomy.

Complications

Diverticulitis may cause fistulas in other organs, leading to pneumaturia, sterile pyuria, fecaluria, or fecal discharge from the vagina. The physician should diagnose with CT and treat with surgical resection.

LARGE BOWEL OBSTRUCTION

Table 2.6-11 describes features that distinguish SBO from large bowel obstruction (LBO).

TABLE 2.6-11. Characteristics of Small and Large Bowel Obstruction

VARIABLE	SMALL BOWEL OBSTRUCTION	LARGE BOWEL OBSTRUCTION
History	Moderate to severe acute abdominal pain; copious emesis Cramping pain with distal SBO Fever, signs of dehydration, and hypotension possible	Constipation/obstipation, deep and cramping abdominal pain (less intense than SBO), nausea/vomiting (less than that of SBO, but more commonly feculent)
Examination	Abdominal distention (distal SBO), abdominal tenderness, visible peristaltic waves, fever, hypovolemia Examination for surgical scars/hernias; rectal examination High-pitched "tinkly" bowel sounds; later, absence of bowel sounds	Significant distention, tympany, and tenderness Examination for peritoneal irritation or mass Fever or signs of shock suggesting perforation/peritonitis or ischemia/necrosis High-pitched "tinkly" bowel sounds; later, absence of bowel sounds
Etiologies	Adhesions (postsurgery), hernias, neoplasm, volvulus, Crohn disease, intussusception, hematoma, foreign body, cystic fibrosis (CF), gallstone ileus	Colon cancer, volvulus, diverticulitis, intussusception, fecal impaction, benign tumors Colon cancer assumed until proven otherwise
Differential	LBO, paralytic ileus, gastroenteritis	SBO, paralytic ileus, appendicitis, IBD, Ogilvie syndrome (pseudo-obstruction)
Diagnosis	CBC, electrolytes, lactic acid, x-ray of the abdomen, contrast studies (determine if it is partial or complete), CT scan	CBC, electrolytes, lactic acid, x-ray of the abdomen, CT scan, water contrast enema (if perforation is suspected), endoscopic evaluation if stable and prior imaging equivocal for bowel perforation
Treatment	Hospitalize. Partial SBO can be treated conservatively with NG decompression, IV fluids, and NPO status. Patients with complete SBO should be managed aggressively with NPO status, NG decompression, IV fluids, electrolyte replacement, and surgical correction. Underlying causes of obstruction (eg hernia or cancer) should be treated as well, if present.	Hospitalize. Obstruction can be relieved with a Gastrografin enema, colonoscopy, or rectal tube; however, surgery is usually required. Ischemic colon usually requires partial colectomy with a diverting colostomy. The physician should treat the underlying cause (eg, neoplasm).

MNEMONIC

3-6-9 Rule of Bowel Dilation

In general, when the bowel is dilated greater than the following dimensions, physicians consider it dilated. Obstruction should be considered.

Small bowel: <3 cm
Large bowel/appendix: <6 cm/<6 mm
Cecum: <9 cm

IRRITABLE BOWEL SYNDROME

Among the most common GI conditions seen in primary care and GI clinics, with a prevalence of 4% to 10%. IBS is an idiopathic functional disorder that commonly affects women in their 20s to 30s. Often patients have comorbid disorders such as depression, anxiety, and fibromyalgia.

History/PE

- Patients with IBS present with abdominal pain that is related to bowel movements, diarrhea and/or constipation, and abdominal distention. Symptoms often worsen with stress. It can be constipation predominant (IBS-C) or diarrheal predominant (IBS-D) or a combination of both.

KEY FACT

Imaging allows identification of small and large bowels according to anatomic locations and appearance. Small bowel: the plicae circularis stand out due to their thin, circular, circumferential mucosal folds. Large bowel: characteristic haustral markings formed by longitudinal and circular muscles.

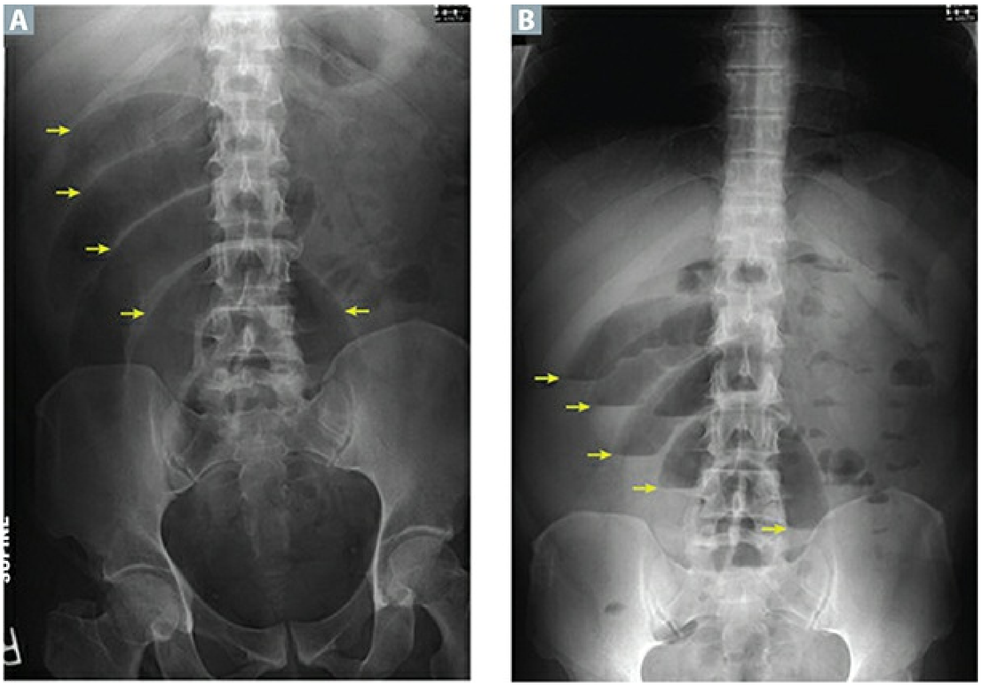


FIGURE 2.6-24. **Abdominal plain films.** Supine **(A)** and upright **(B)** abdominal plain films demonstrate multiple loops of dilated small bowel *(arrows in A)* with air/fluid levels *(arrows in B)* in the right abdomen, suggestive of small bowel obstruction; this finding can also be seen as an unusual sign of acute appendicitis. Intestinal malrotation was not considered at this time. (Reproduced with permission from Welte FJ, Grosso M. Left-sided appendicitis in a patient with congenital gastrointestinal malrotation: A case report. *J Med Case Rep*. 2007;1:92..)

- **No alarm symptoms:** Rarely awakens patients from sleep. Vomiting, significant weight loss, hematochezia, and constitutional symptoms are uncommon.
- **PE:** Usually unremarkable.

Diagnosis

- **Definition (per Rome IV diagnostic criteria):** At least 4 days in 2 months of episodic abdominal discomfort that is (one or more of the following criteria): (1) related to defecation; (2) associated with a change in stool frequency or consistency; (3) associated with a change in stool appearance.
- There are no biomarkers or diagnostic tests currently available for IBS. Celiac disease should be ruled out in diarrhea-predominant IBS.

- In children, usually abdominal pain that is not resolved with resolution of constipation.
- After appropriate evaluation, symptoms not fully explained by another medical condition.

Treatment

- **Psychosocial:** Patients benefit from a strong patient-physician relationship. Physicians should offer reassurance and should not dismiss the symptoms.
- **Lifestyle:** Consistent physical activity in the form of exercise has been shown to reduce severity of IBS-related symptoms.
- **Diet:** Patients should avoid insoluble fiber and supplement their diets with soluble fiber (found in psyllium, oat bran, barley, and beans).
- Chronic constipation may lead to anal fissures. Treat with topical anesthetics and vasodilators.
- **Pharmacologic:** Initial treatment includes soluble fiber and antispasmodics for global IBS symptoms. Symptomatic treatment of IBS-C may include use of chloride channel activators (lubiprostone) or guanylate cyclase activators (linaclotide, plecanatide). Rifaximin may be used for treatment of IBS-D. Neuromodulators (eg, TCA/SNRI [serotonin-norepinephrine reuptake inhibitor]) may be used to treat both IBS-C and IBS-D.

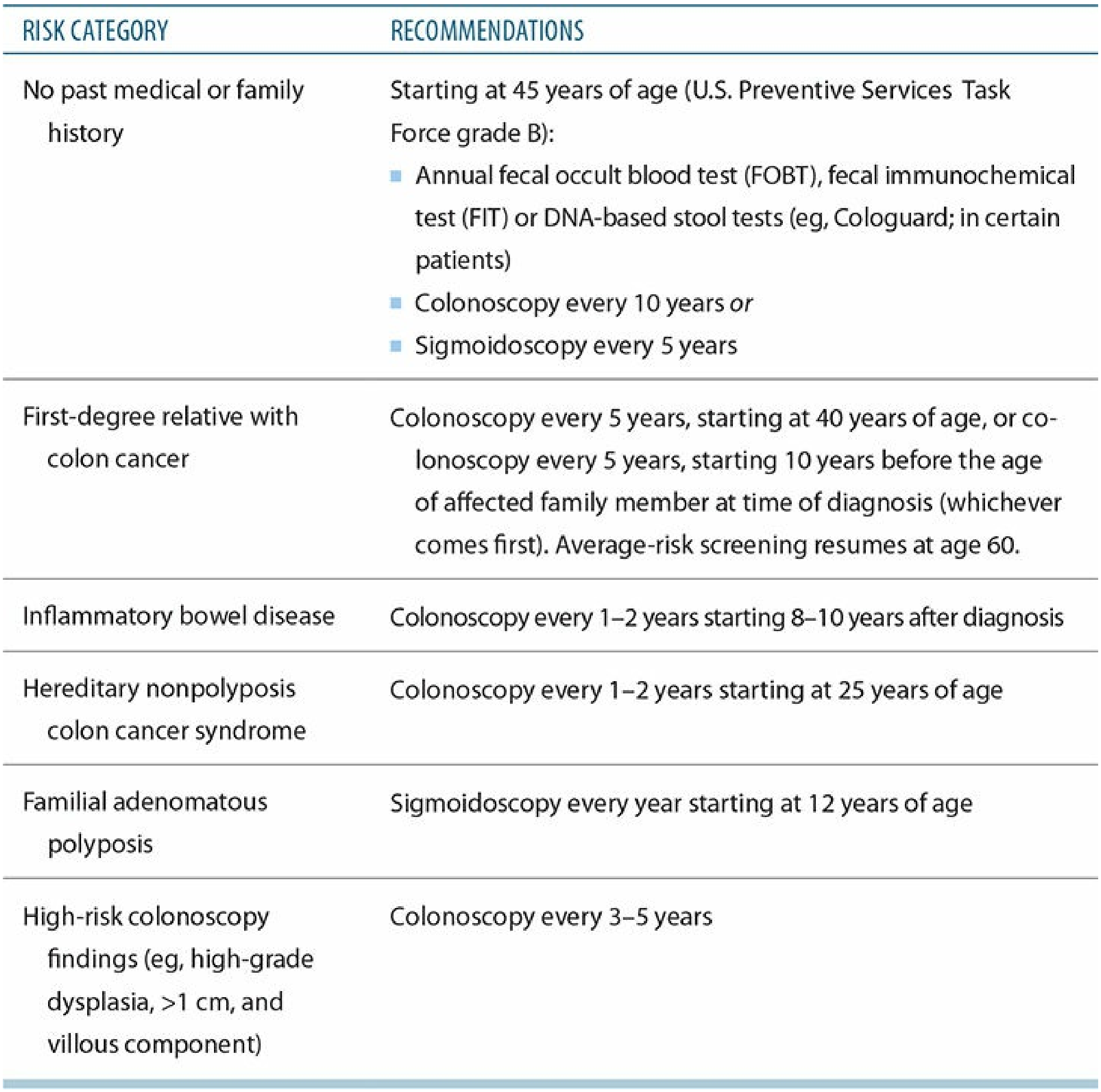
COLORECTAL CANCER

The second leading cause of cancer mortality in the United States. There is an ↑ incidence with age, with a peak incidence at 70 to 80 years of age. Risk factors and screening recommendations are summarized in Tables 2.6-12 and 2.6-13.

TABLE 2.6-12. **Risk Factors for Colorectal Cancer**

RISK FACTOR	COMMENTS
Age	Risk ↑ with age; peak incidence is at 70–80 years of age
Hereditary polyposis syndromes	Familial adenomatous polyposis (FAP; 100% risk by 40 years of age); hereditary nonpolyposis colorectal cancer (HNPCC, also known as Lynch syndrome. Also risk for endometrial and ovarian cancers.)
⊕ Family history	Especially first-degree relatives < 60 years of age
IBD	Ulcerative colitis > Crohn disease
Adenomatous polyps	Villous > tubular; sessile > pedunculated
High-fat, low-fiber diet, alcohol, and sedentary lifestyle	—

TABLE 2.6-13. **Screening Recommendations for Colorectal Cancer**



RISK CATEGORY	RECOMMENDATIONS
No past medical or family history	Starting at 45 years of age (U.S. Preventive Services Task Force grade B): ■ Annual fecal occult blood test (FOBT), fecal immunochemical test (FIT) or DNA-based stool tests (eg, Cologuard; in certain patients) ■ Colonoscopy every 10 years *or* ■ Sigmoidoscopy every 5 years
First-degree relative with colon cancer	Colonoscopy every 5 years, starting at 40 years of age, or colonoscopy every 5 years, starting 10 years before the age of affected family member at time of diagnosis (whichever comes first). Average-risk screening resumes at age 60.
Inflammatory bowel disease	Colonoscopy every 1–2 years starting 8–10 years after diagnosis
Hereditary nonpolyposis colon cancer syndrome	Colonoscopy every 1–2 years starting at 25 years of age
Familial adenomatous polyposis	Sigmoidoscopy every year starting at 12 years of age
High-risk colonoscopy findings (eg, high-grade dysplasia, >1 cm, and villous component)	Colonoscopy every 3–5 years

History/PE

Most patients are asymptomatic. In those who have symptoms, the location of the lesion varies.

- **Right-sided lesions:** Often bulky, ulcerating, exophytic masses that lead to anemia from chronic occult blood loss. Patients may complain of weight loss, anorexia, diarrhea, weakness, or vague abdominal pain. Obstruction is rare. (Right colon has a larger diameter than left colon.)
- **Left-sided lesions:** Typically, “apple-core” obstructing masses (see Fig. 2.6-25). Patients complain of obstruction, change in bowel habits (eg, ↓ stool caliber, constipation, obstipation), and/or blood-streaked stools. (Left side has smaller diameter and thus is easier to obstruct.)

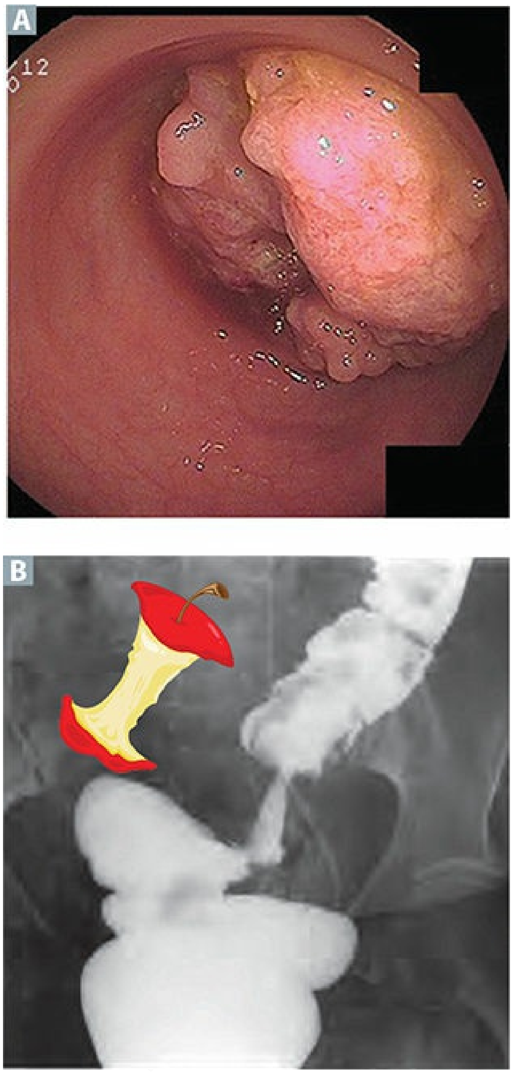


FIGURE 2.6-25. **A carcinoma seen in the ascending colon during colonoscopy (A) and apple-core lesion seen on contrast enema imaging (B).** (Image A adapted with permission from Takiyama A, Nozawa H, Ishihara S, et al. Secondary metastasis in the lymph node of the bowel invaded by colon cancer: A report of three cases. *World J Surg Oncol.* 2016;14[1]:273. Published 2016 Oct 26. Image B reproduced with permission from USMLE-Rx.com.)

- **Rectal lesions:** Usually present with bright-red blood per rectum, often with tenesmus and/or rectal pain. Rectal cancer must be ruled out in all patients with rectal bleeding. However, ⊖ fecal occult blood test (FOBT) has insufficient sensitivity to exclude the possibility of cancer.

Diagnosis

- **Most accurate test:** Colonoscopy with biopsy
- **Evaluation for metastases:** CXR, liver function tests (LFTs), and an abdominal/pelvic CT
- Staging based on the depth of tumor penetration into the bowel wall and the presence of lymph node involvement and distant metastases

KEY FACT

Iron-deficiency anemia in an older adult patient indicates colorectal cancer until proven otherwise.

Treatment

- **Best initial treatment:** Surgical resection of the tumor (colectomy of varying length depending on tumor size) ± radiation for rectal cancer
- Neoadjuvant chemotherapy and/or radiotherapy usually administered to reduce tumor burden
- Follow-up with serial carcinoembryonic antigen (CEA) levels to detect recurrence; colonoscopy 1 year after resection and every 3 to 5 years thereafter; LFTs, CXR, and abdominal CT to screen for metastases

COLORECTAL CANCER-ASSOCIATED CONDITIONS

Several genetically linked diseases may increase the risk of lower intestinal malignancy, including Lynch syndrome, Peutz-Jeghers syndrome, Gardner syndrome, Turcot syndrome, and juvenile polyposis syndrome.

Lynch Syndrome

Also called hereditary nonpolyposis colorectal cancer (HNPCC). Autosomal dominant disease that increases risk for **C**olorectal, **E**ndometrial, **O**varian ("**CEO**") cancers due to a mismatch-repair gene deficiency (eg, *MSH2, MLH1*, *MSH6*, *PMS2*, and *EPCAM*).

Q

A 60-year-old patient with no past medical history presents with fever, dyspnea, and orthopnea of 2 weeks' duration. Physical examination reveals splinter hemorrhages and a new IV/VI diastolic decrescendo murmur. Echocardiogram confirms aortic valve endocarditis, and IV antibiotics are started. Blood cultures are ⊕ for *Streptococcus bovis.* What is the next diagnostic step?

- ***Hx/PE:*** Patient aged <50 years with positive family history of colorectal (eg, three or more members) or associated cancers
- ***Dx:*** Genetic testing for most commonly mutated genes (listed earlier)
- ***Tx:*** Colonoscopy every 1 to 2 years starting at age 20 to 25 years or 5 years prior to earliest family Lynch diagnosis

Peutz-Jeghers Syndrome

Autosomal dominant disease that leads to benign, hamartomatous polyps. Although polyps are benign, patients remain at higher risk for GI, breast, and gynecologic cancers.

- ***Hx/PE:*** Numerous mucocutaneous pigmented macules and possibly a family history of the associated cancers
- ***Dx:*** Diagnosis with two of three clinical history criteria: family history of Peutz-Jeghers, presence of hyperpigmented macules (see Fig. 2.6-26), and/or hamartomatous polyps found in GI tract

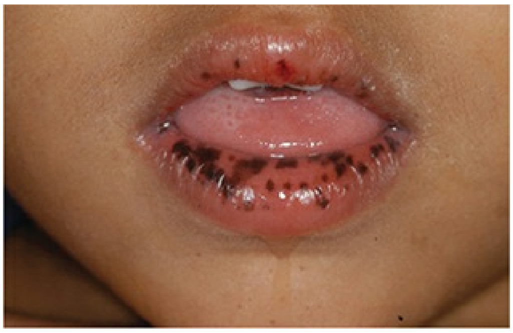


FIGURE 2.6-26. **A classic finding of Peutz-Jeghers syndrome: pigmented macules on oral mucosa.** (Reproduced with permission from Gondak RO, da Silva-Jorge R, Jorge J, Lopes MA, Vargas PA. Oral pigmented lesions: Clinicopathologic features and review of the literature. *Med Oral Patol Oral Cir Bucal.* 2012;17[6]:e919-e924.)

- ***Tx:*** Requires GI cancer screening at diagnosis (EGD, video capsule endoscopy, and colonoscopy) with subsequent screening based on presence of polyps

Gardner Syndrome

Familial adenomatous polyposis (FAP) + osteomas + fibromatosis

- ***Hx/PE:*** Painless bone growths typically on the skull or facial bones. Unerupted teeth. Dermal manifestations such as lipomas or fibromas. Fundoscopy showing hypertrophy of retinal pigment epithelium.
- ***Dx:*** Occurs through genetic testing or presence of >100 colorectal polyps and classic skin and bone findings.
- ***Tx:*** Screening for GI cancer with sigmoidoscopy every year, starting at 12 years of age (similar to that of FAP).

Turcot Syndrome

FAP + brain tumors (eg, medulloblastoma)

- ***Hx/PE:*** Signs of neurologic deficit in the setting of positive family history or >100 polyps found on colonoscopy
- ***Dx:*** Genetic testing for APC mutation or mismatch-repair gene mutations (eg, *MLH1* and *PMS2*)
- ***Tx:*** Similar screening to FAP, as well as neurologic screenings (brain imaging for screening not typically done)

Juvenile Polyposis Syndrome (JPS)

Autosomal dominant condition causing numerous hamartomatous polyps in the GI tract in young patients.

- ***Hx/PE:*** Most commonly presents in a young adult (<20 years) with rectal bleeding or signs of anemia. May also have signs of obstruction or frequent diarrhea.
- ***Dx:*** Endoscopy revealing one or more of the following: single polyp in someone with family history of JPS, >5 polyps found in colorectum, or multiple polyps anywhere else in GI tract.
- ***Tx:*** Colonoscopy every 1 to 3 years or yearly if polyps are found; upper endoscopy every 2 to 3 years or yearly if polyps are found.

Colonoscopy is the next diagnostic step. Although the mechanism of association has yet to be determined, there is a well-established association between *S. bovis* and colon cancer. *Clostridium septicum* is also associated with colon cancer.

ISCHEMIC COLITIS

Insufficient blood supply to the colon that results in ischemia and, potentially, necrosis. Most commonly affects the left colon, particularly the "watershed area" at the splenic flexure (see Fig. 2.6-27 for anatomic illustration of watershed areas of the colon). Usually occurs in the setting of atherosclerosis.

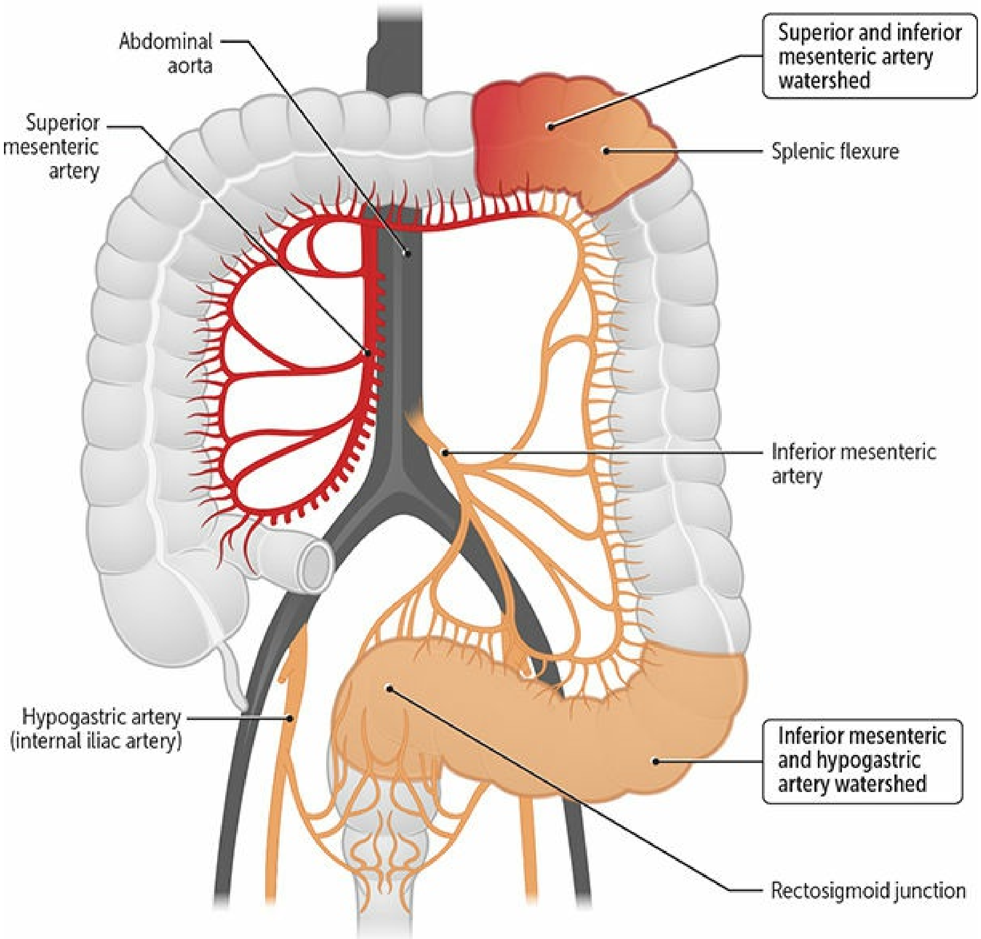

Abdominal aorta
Superior mesenteric artery
Superior and inferior mesenteric artery watershed
Splenic flexure
Inferior mesenteric artery
Hypogastric artery (internal iliac artery)
Inferior mesenteric and hypogastric artery watershed
Rectosigmoid junction

FIGURE 2.6-27. **Watershed areas of the GI tract.** (Reproduced with permission from USMLE-Rx.com.)

History/PE

- Presents with crampy lower abdominal pain followed by bloody diarrhea after meals or exertion or in the heat. Fever and peritoneal signs suggest bowel necrosis.
- ***Risk factors:*** Surgery that may reduce blood flow to colon (eg, AAA repair, coronary artery bypass), atherosclerosis risk factors (eg, diabetes and hypertension), hypercoagulability, and constipation.

Differential

- Acute mesenteric ischemia: History more suggestive of a thrombus or embolus in the setting of arrythmia or long-standing atherosclerosis. Infarction is not localized to

watershed areas.
- Chronic mesenteric ischemia: Less acute presentation than ischemic colitis. Patient has history of food aversion due to postprandial pain.

Diagnosis

- **Best initial test:** CT scan with contrast possibly showing thickened bowel wall, atherosclerosis
- **Most accurate test:** Angiography
- Colonoscopy possibly showing a pale mucosa with petechial bleeding

Treatment

- Supportive therapy with bowel rest, IV fluids, and broad-spectrum antibiotics
- Surgical bowel resection indicated for infarction, fulminant colitis, or obstruction

MICROSCOPIC COLITIS

Chronic, inflammatory cause of diarrhea subdivided into lymphocytic and collagenous colitis.

History/PE

The typical patient is a middle-aged adult with chronic, watery diarrhea who has negative workup for other etiologies.

Diagnosis

Evaluation of other causes typically precedes the required colonic biopsy to diagnose (eg, infectious, celiac, Crohn disease). Colonoscopy classically shows normal mucosa. Biopsy will show subepithelial collagen if the patient has a collagenous variant; alternatively, the biopsy will show intraepithelial lymphocytes if the lymphocytic variant.

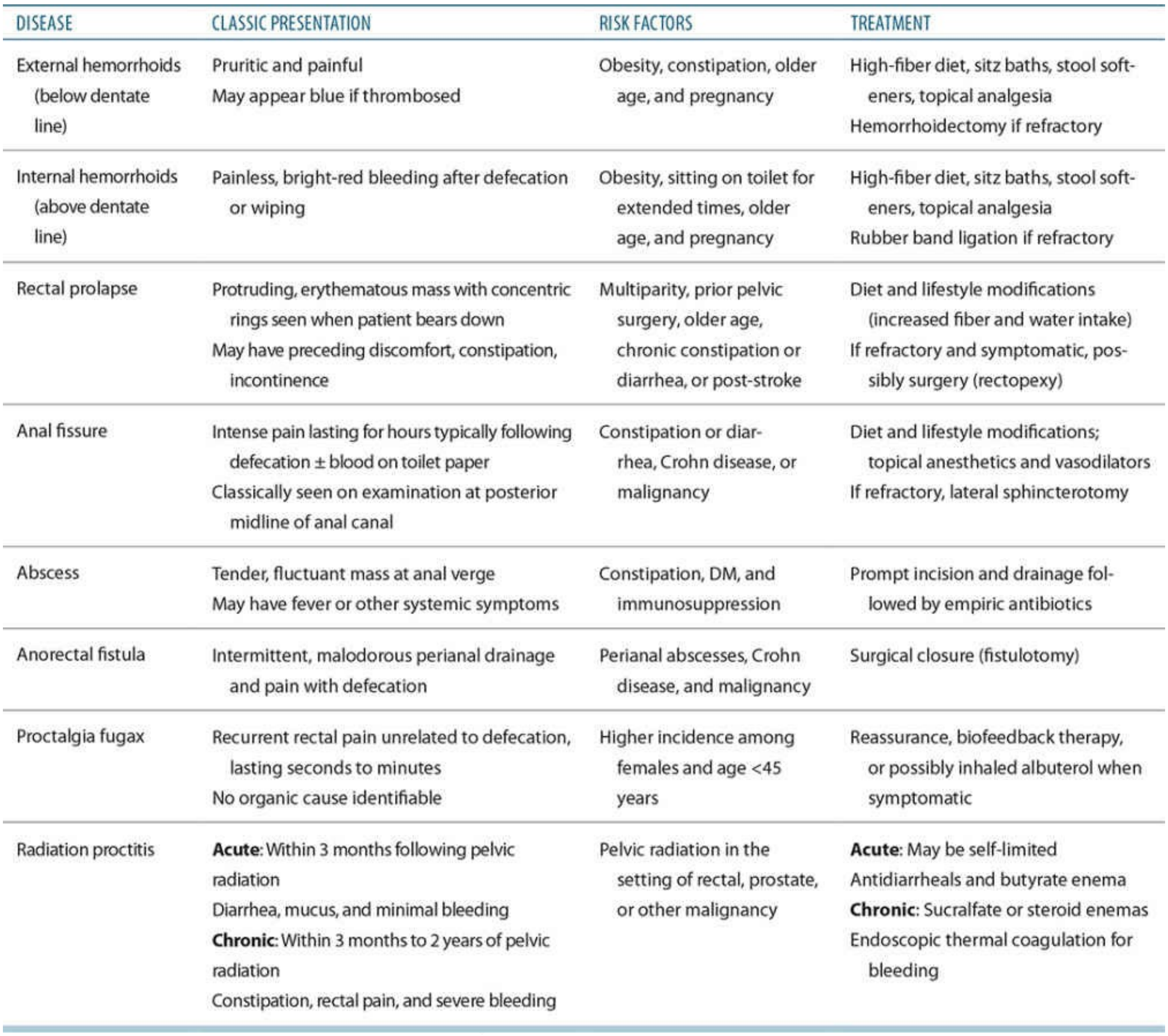
Treatment

The patient should avoid trigger medications (eg, NSAIDs, sertraline, PPIs). Supplemental antidiarrheals and short courses of glucocorticoids may be used if refractory.

ANORECTAL DISEASE

The rectum and anus have diverse pathology that can cause significant symptoms for patients, which can be distinguished based on presentation, exam, and risk factors (Table 2.6-14).

TABLE 2.6-14. **Differentiating Anorectal Diseases**



DISEASE	CLASSIC PRESENTATION	RISK FACTORS	TREATMENT
External hemorrhoids (below dentate line)	Pruritic and painful May appear blue if thrombosed	Obesity, constipation, older age, and pregnancy	High-fiber diet, sitz baths, stool softeners, topical analgesia Hemorrhoidectomy if refractory
Internal hemorrhoids (above dentate line)	Painless, bright-red bleeding after defecation or wiping	Obesity, sitting on toilet for extended times, older age, and pregnancy	High-fiber diet, sitz baths, stool softeners, topical analgesia Rubber band ligation if refractory
Rectal prolapse	Protruding, erythematous mass with concentric rings seen when patient bears down May have preceding discomfort, constipation, incontinence	Multiparity, prior pelvic surgery, older age, chronic constipation or diarrhea, or post-stroke	Diet and lifestyle modifications (increased fiber and water intake) If refractory and symptomatic, possibly surgery (rectopexy)
Anal fissure	Intense pain lasting for hours typically following defecation ± blood on toilet paper Classically seen on examination at posterior midline of anal canal	Constipation or diarrhea, Crohn disease, or malignancy	Diet and lifestyle modifications; topical anesthetics and vasodilators If refractory, lateral sphincterotomy
Abscess	Tender, fluctuant mass at anal verge May have fever or other systemic symptoms	Constipation, DM, and immunosuppression	Prompt incision and drainage followed by empiric antibiotics
Anorectal fistula	Intermittent, malodorous perianal drainage and pain with defecation	Perianal abscesses, Crohn disease, and malignancy	Surgical closure (fistulotomy)
Proctalgia fugax	Recurrent rectal pain unrelated to defecation, lasting seconds to minutes No organic cause identifiable	Higher incidence among females and age <45 years	Reassurance, biofeedback therapy, or possibly inhaled albuterol when symptomatic
Radiation proctitis	**Acute**: Within 3 months following pelvic radiation Diarrhea, mucus, and minimal bleeding **Chronic**: Within 3 months to 2 years of pelvic radiation Constipation, rectal pain, and severe bleeding	Pelvic radiation in the setting of rectal, prostate, or other malignancy	**Acute**: May be self-limited Antidiarrheals and butyrate enema **Chronic**: Sucralfate or steroid enemas Endoscopic thermal coagulation for bleeding

HEMORRHOID GRADING

I – Enlarged vasculature without prolapse
II – Reducible prolapse that occurs only with straining
III – Manually reproducible prolapse that extends below the dentate line
IV – Prolapse that cannot be reduced

INFLAMMATORY BOWEL DISEASE

Includes Crohn disease (see Fig. 2.6-28) and ulcerative colitis (see Fig. 2.6-29). See Table 2.6-15 for differentiation between the two diseases. See Figure 2.6-30 for anatomic distribution of diseases. Most common in Caucasians and those of Ashkenazi Jewish decent, with onset most frequently occurring in the teens to 50s. Table 2.6-9 summarizes the features of IBD. In patients with a history of Crohn disease and acute abdominal pain, the physician should suspect SBO, which is caused by transmural inflammation and stricture formation. Transmural inflammation in Crohn disease can also lead to fistula formation, abscesses, and draining sinuses. Ulcerative colitis does not cause fistulas.

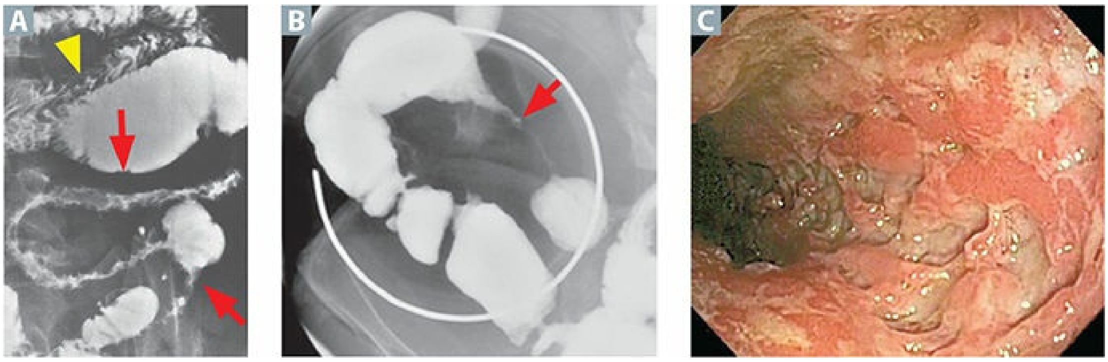


FIGURE 2.6-28. Crohn disease. (A) Small bowel follow-through (SBFT) barium study shows skip areas of narrowed small bowel with nodular mucosa *(arrows)* and ulceration. Compare with normal small bowel *(arrowhead)*. **(B)** Spot compression image from SBFT shows "string sign" narrowing *(arrow)* caused by stricture. **(C)** Deep ulcers in the colon of a patient with Crohn disease, seen at colonoscopy. (Image A reproduced with permission from Chen MY et al. *Basic Radiology*. New York, NY: McGraw-Hill; 2004. Image B reproduced with permission from USMLE-Rx.com. Image C reproduced with permission from Fauci AS et al. *Harrison's Principles of Internal* Medicine, 17th ed. New York, NY: McGraw-Hill; 2008).

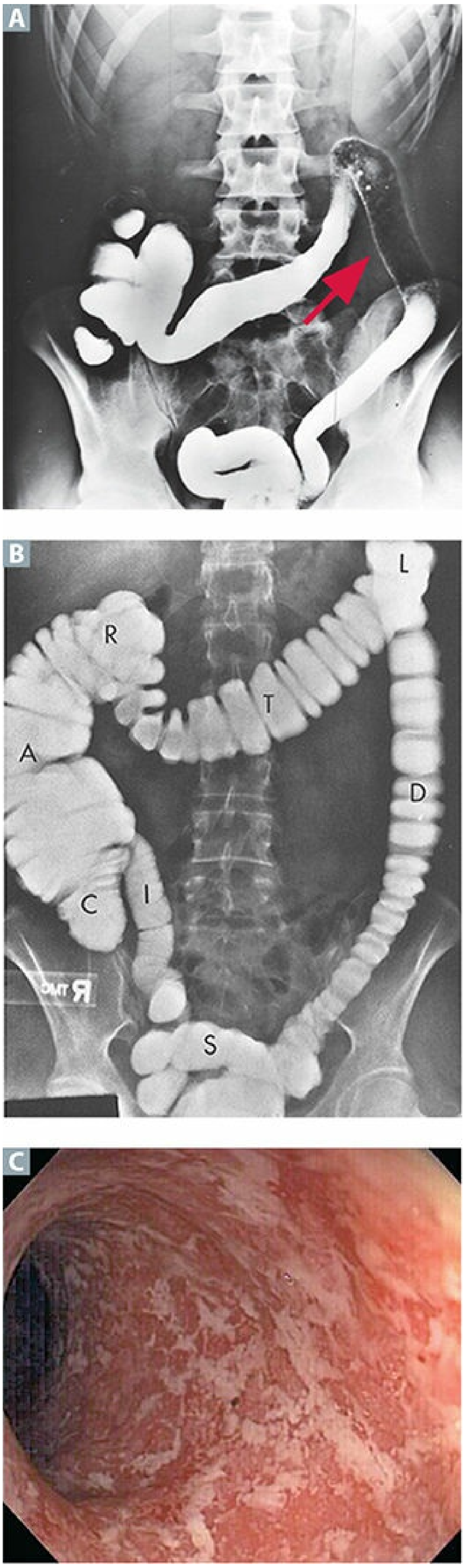


FIGURE 2.6-29. **Ulcerative colitis. (A)** X-ray from a barium enema showing a featureless ("lead pipe") colon with small mucosal ulcerations *(arrow)*. Compare with normal haustral markings in **(B). (C)** Diffuse mucosal ulcerations and exudates at colonoscopy in chronic

ulcerative colitis. (Image A reproduced with permission from Doherty GM. *Current Diagnosis & Treatment:* Surgery, 13th ed. New York, NY: McGraw-Hill; 2010. Image B reproduced with permission from Chen MY et al. *Basic Radiology*. New York, NY: McGraw-Hill; 2004. Image C reproduced with permission from Fauci AS et al. *Harrison's Principles of Internal* Medicine, 17th ed. New York, NY: McGraw-Hill; 2008.)

TABLE 2.6-15. Features of Ulcerative Colitis and Crohn Disease

VARIABLE	ULCERATIVE COLITIS	CROHN DISEASE
Site of involvement	Rectum always involved. May extend proximally in a continuous fashion. In most cases only involves the colon. Inflammation and ulceration limited to the mucosa and submucosa	May involve any portion of the GI tract, particularly the ileocecal region, in a discontinuous pattern ("skip lesions"); rectum is often spared Transmural inflammation is seen, sometimes leading to fistulas to other organs
History/ examination	Bloody diarrhea, lower abdominal cramps, tenesmus, urgency Exam possibly revealing orthostatic hypotension, tachycardia, abdominal tenderness, frank blood on rectal exam, and extraintestinal manifestations Toxic megacolon possibly presented (avoidance of tubes or scopes in view of the risk for perforation)	Abdominal pain, abdominal mass, low-grade fever, weight loss, watery diarrhea Exam may reveal fever, abdominal tenderness or mass, perianal fissures or tags, fistulas, and extraintestinal manifestations
Extraintestinal manifestations	Aphthous stomatitis, episcleritis/uveitis, arthritis, primary sclerosing cholangitis, erythema nodosum, and pyoderma gangrenosum	Same as ulcerative colitis (UC) in addition to fistulas to the skin, to the bladder, or between bowel loops
Diagnosis	CBC, x-ray of the abdomen, stool cultures, O&P, stool assay for *C difficile* Colonoscopy possibly showing diffuse and continuous rectal involvement, friability, edema, and pseudopolyps Definitive diagnosis with biopsy	Same lab workup as for UC; upper GI series with small bowel follow-through Colonoscopy possibly showing aphthoid, linear, or stellate ulcers; strictures; noncaseating granulomas, "cobblestoning," and "skip lesions" "Creeping fat" possibly present during laparotomy Definitive diagnosis with biopsy
Treatment	5-acetylsalicylic acid (ASA) agents (eg, sulfasalazine, mesalamine), topical or oral; corticosteroids for flare-ups and immunomodulators (eg, azathioprine) or biologics (eg, infliximab) for refractory or moderate to severe disease Total proctocolectomy possibly curative for long-standing or fulminant colitis or toxic megacolon; also ↓ cancer risk	Similar to UC: Corticosteroids for flare-ups. May require biologics (eg, infliximab) (first-line) or immunomodulators (eg, azathioprine) for refractory or moderate to severe disease and for maintenance therapy Surgical resection potentially necessary for suspected perforation, stricture, fistula, or abscess
Incidence of cancer	Markedly ↑ risk for colorectal cancer in long-standing cases (monitor with frequent FOBT and yearly colonoscopy with multiple biopsies after 8 years of disease)	Incidence of secondary malignancy lower than that for UC but greater than that of the general population

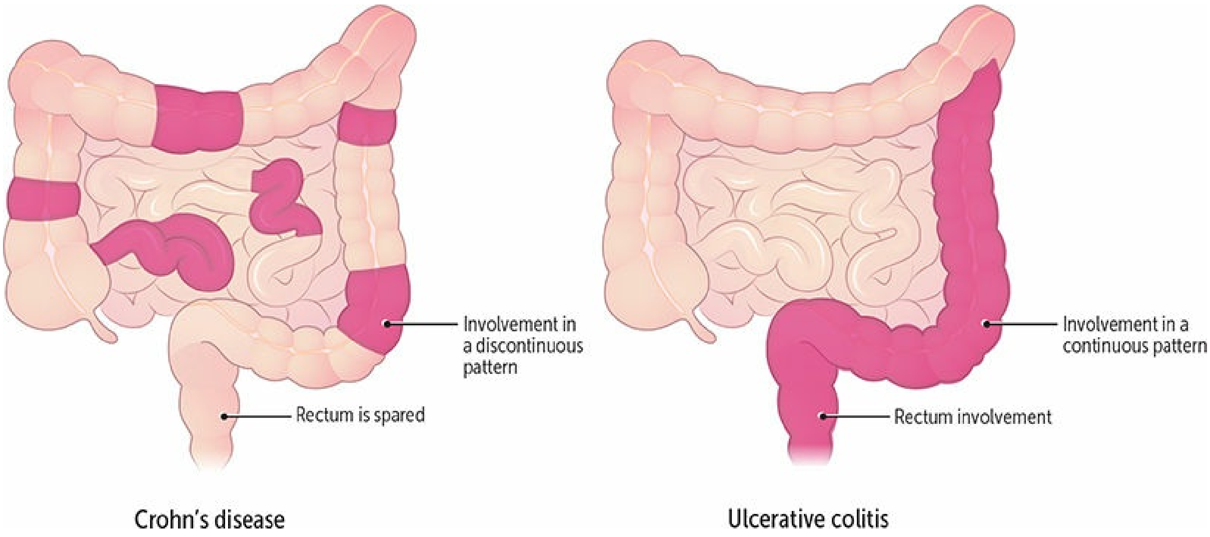

Involvement in a discontinuous pattern
Rectum is spared
Crohn's disease
Involvement in a continuous pattern
Rectum involvement
Ulcerative colitis

FIGURE 2.6-30. **Crohn disease vs ulcerative colitis distribution throughout the GI tract.** (Reproduced with permission from USMLE-Rx.com.)

HERNIAS

Inguinal hernias are protrusions of abdominal contents (usually the small intestine) into the inguinal region through a weakness or defect in the abdominal wall. See Table 2.6-16 for comparisons of several different types of common hernias, including inguinal hernias.

TABLE 2.6-16. **Types of Hernias**

HERNIA TYPE	LOCATION	ETIOLOGY	PREVALENCE
Indirect	Herniation of abdominal contents through both external and internal rings, lateral to inferior epigastric vessels (see Fig. 2.6-36)	Results from congenital patent processus vaginalis	Most common
Direct	Herniation through floor of Hesselbach triangle, medial to epigastric vessels (see Fig. 2.6-36)	Mechanical breakdown in transversalis fascia resulting from older age	
Femoral	Herniation below inguinal ligament through femoral canal, below and lateral to the pubic tubercle	Increased intra-abdominal pressure, weakened pelvic floor	More common in females than in males
Incisional	Herniation through the site of a previous surgical incision (incisional hernia)	Localized, mechanical weakness of the abdominal wall from prior abdominal incision Risk factors: Patient factors (older age, smoking, obesity, immunosuppression, connective tissue disease) and technical factors (wound infection, suboptimal closure, fascial dehiscence, larger open, as opposed to laparoscopic, surgeries)	Most commonly occurs after midline abdominal incisions
Spigelian	Just lateral to the lateral border of the rectus muscle	Caused by a defect in the spigelian aponeurosis that is composed of the transversus	Usually occur in the fifth or sixth decades of life; rare
Umbilical	Center of the umbilical ring	Typically caused by herniation of omentum or peritoneal fat through the umbilical ring; bowel can herniate through here as well Risk factors: Obesity, abdominal distention, ascites, pregnancy	More common in females, but more likely to present incarcerated in males
Epigastric	Midline between the umbilicus and the xiphoid process	Thought to be due to a congenitally weakened linea alba Risk factors: Extensive physical training, coughing, obesity, smoking, chronic steroid use, diabetes, older age, and male sex	More common in males; rare

KEY FACT

Epigastric, umbilical, and anterior incisional hernias are all types of ventral hernias.

KEY FACT

The Hesselbach triangle is an area bounded by the inguinal ligament, the inferior epigastric artery, and the rectus abdominis.

Treatment

Because of the risk for incarceration and strangulation, surgical correction is indicated.

BILIARY DISEASE

CHOLELITHIASIS AND BILIARY COLIC

Colic results from transient cystic duct blockage from impacted stones. Although risk factors include the **four Fs** (**F**emale, **F**at, **F**ertile, and **F**orty), the disorder is common and can occur in any patient. Additional risk factors include use of oral contraceptive pills (OCPs), rapid weight loss, chronic hemolysis (pigment stones in sickle cell disease), small bowel resection (loss of enterohepatically circulated bile), and TPN. Table 2.6-17 details the forms of biliary disease and compares the laboratory findings associated with each one.

TABLE 2.6-17. **Disorders Caused by Gallstones**

DISORDER	DEFINITION	PRESENTATION	LABORATORY RESULTS	DIAGNOSIS	MANAGEMENT
Cholelithiasis	Stones in the gallbladder	May be asymptomatic, or may cause biliary colic; transient RUQ pain commonly seen after eating fatty meals; caused by temporary occlusion of the cystic duct by a stone	Normal total bilirubin/alkaline phosphatase, serum amylase	Ultrasonography	If asymptomatic, observation; if symptomatic, laparoscopic cholecystectomy
Cholecystitis	Inflammation of the gallbladder, typically caused by stone occluding the cystic duct	RUQ pain, fever (maybe), Murphy sign (cessation of inspiration with palpation of RUQ) Tends to present in critically ill patients, typically in the ICU	↑ WBC, normal total bilirubin/alkaline phosphatase, amylase	Ultrasonography, hepato-iminodiacetic acid (HIDA) scan	Laparoscopic cholecystectomy; if patient is too ill to undergo surgery, transcutaneous drainage of gallbladder
Choledocholithiasis	Stone in the common bile duct (CBD)	Jaundice, ± RUQ pain, afebrile	Normal/↑ WBC, ↑ total bilirubin/alkaline phosphatase, ↑ amylase/lipase (if pancreatitis is present)	Ultrasonography often does not show the stone but may show dilated CBD. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) are definitive	Endoscopic retrograde cholangiopancreatography (ERCP) to remove stone, followed by cholecystectomy
Cholangitis	Infection of the CBD, usually caused by stone in the CBD	Charcot triad: RUQ pain, fever, jaundice, Reynolds pentad: Charcot triad + shock and altered mental status	↑ WBC, ↑ total bilirubin/alkaline phosphatase	Clinical diagnosis confirmed by biliary dilation on imaging; or ERCP (both diagnostic and therapeutic)	ERCP; surgery if patient toxic

History/PE

- Postprandial abdominal pain (usually in the RUQ) that radiates to the right subscapular area or the epigastrium, often associated with nausea and vomiting, dyspepsia, and flatulence
- **Gallstones:** May have RUQ tenderness and a palpable gallbladder or be asymptomatic

MNEMONIC

MDs don’t Lie

Medial to inferior epigastric vessel = **D**irect hernia
Lateral to epigastric vessel = **I**ndirect hernia

KEY FACT

Immunosuppressed patients (especially patients with diabetes) are at risk for emphysematous cholecystitis (infection of the gallbladder with gas-forming bacteria). This requires emergent chol-ecystectomy.

Diagnosis

RUQ ultrasound is the best initial test and the most accurate test (see Fig. 2.6-31).

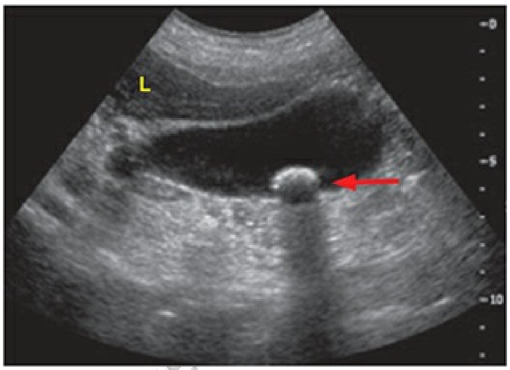


FIGURE 2.6-31. **Cholelithiasis.** Ultrasound image of the gallbladder shows a gallstone *(arrow)* with posterior shadowing. *L*, Liver. (Reproduced with permission from USMLE-Rx.com.)

Treatment

- Cholecystectomy is curative and recommended for patients with symptomatic gallstones. Asymptomatic gallstones do not require treatment. Lifestyle modifications may help aid in asymptomatic gallstone elimination (eg, reduced refined carbohydrates, adequate fiber intake, glycemic control in people with diabetes, weight loss at a modest pace).
- Porcelain gallbladder (PGB), characterized by gallbladder calcification, is often (but not always) asymptomatic and discovered incidentally. Risk of gallbladder adenocarcinoma is increased. Cholecystectomy is indicated if symptomatic or asymptomatic with high-risk features (eg, spotty calcification) or low procedural risk (eg, young and fit).

Complications

Postcholecystectomy syndrome can stem from retained stones, strictures, or extrabiliary causes. Symptoms include early satiety, bloating, and dyspepsia after cholecystectomy. Diagnosis is made with additional abdominal imaging (ultrasound, endoscopic retrograde cholangiopancreatography [ERCP], magnetic resonance cholangiopancreatography [MRCP]).

CHOLECYSTITIS

Prolonged blockage of the cystic duct by a gallstone, which leads to progressive distention, inflammation, and infection. Acalculous cholecystitis occurs in the absence of cholelithiasis in patients who are chronically debilitated or critically ill.

History/PE

- **History:** RUQ pain, nausea, vomiting, and fever. See Figure 2.6-32 for ultrasound findings consistent with acute cholecystitis.

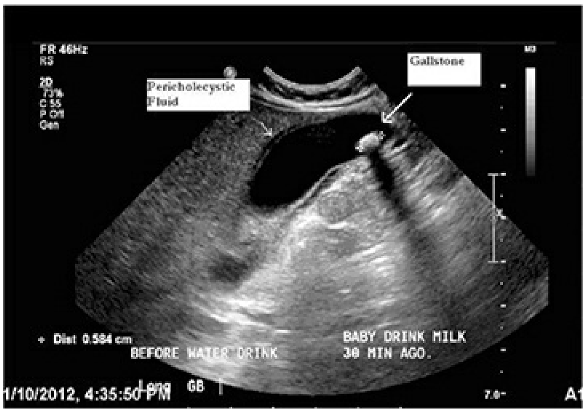


FIGURE 2.6-32. **Cholecystitis.** RUQ ultrasound imaging of acute cholecystitis revealing pericholecystic fluid with a gallstone visualized within the gallbladder lumen. (Reproduced with permission from Nibhanipudi K, Al-Husaini A, Kahlon S, Stone RK. An unusual cause of vomiting in an infant of 3 months of age. *Case Rep Emerg Med.* 2012;2012:913481.)

- **Physical exam:** RUQ tenderness, inspiratory arrest with deep palpation of the RUQ (Murphy sign), and low-grade fever.

Q

A 43-year-old patient presents to the emergency department with nausea, vomiting, and epigastric pain. They have complained of intermittent RUQ pain for the past several months. Physical examination reveals marked epigastric tenderness. Labs show leukocytosis, ↑ aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and ↑ lipase. X-ray of the abdomen is unremarkable. What is the most likely diagnosis?

Diagnosis

- **Best initial test:** Ultrasound may reveal stones, bile sludge, pericholecystic fluid, a thickened gallbladder wall, gas in the wall of the gallbladder, and/or an ultrasonic Murphy sign.
- If ultrasound is equivocal, the next best step is a hepato-iminodiacetic acid (HIDA) scan. A nuclear imaging tool, it uses a radiotracer excreted through the biliary system. On HIDA, nonvisualization of the gallbladder suggests acute cholecystitis.

Treatment

- Broad-spectrum IV antibiotics and IV fluids
- Cholecystectomy indicated

CHOLEDOCHOLITHIASIS

Gallstones in the common bile duct (CBD). Symptoms vary according to the degree of obstruction, the duration of the obstruction, and the presence/severity of infection.

- ***Hx/PE:*** Biliary colic, jaundice, afebrile unless current infection, and/or pancreatitis
- ***Dx:*** ↑ alkaline phosphatase and total and direct bilirubin (see Table 2.6-17)
- ***Tx:*** ERCP with sphincterotomy followed by cholecystectomy

CHOLANGITIS

- An acute bacterial infection of the biliary tree that commonly occurs secondary to obstruction, usually from gallstones (choledocholithiasis).
- **Other etiologies:** Bile duct stricture, primary sclerosing cholangitis (PSC), and malignancy. Gram ⊖ enterics commonly identified pathogen.

History/PE

- Charcot triad—RUQ pain, jaundice, and fever/chills—is classic.
- Reynolds pentad—Charcot triad plus septic shock and altered mental status—may be present in acute suppurative cholangitis.

Diagnosis

- **Labs:** Leukocytosis, ↑ bilirubin, and ↑ alkaline phosphatase (see Table 2.6-17); blood cultures
- **Best initial test:** Ultrasound diagnostic for CBD dilation
- **Most accurate test:** ERCP diagnostic and therapeutic

Treatment

- Patients often require ICU admission for monitoring, hydration, BP support, and broad-spectrum IV antibiotic treatment.
- Patients with acute suppurative cholangitis require emergent bile duct decompression via ERCP/sphincterotomy, percutaneous transhepatic drainage, or open decompression.

A

The most likely diagnosis is gallstone pancreatitis, which results from a gallstone that travels through the common bile duct (CBD) and lodges at the ampulla of Vater, thus obstructing the flow of both pancreatic exocrine enzymes and bile. It most commonly occurs in females, who often report a history of biliary colic. Treatment involves management of the pancreatitis with supportive care and elective cholecystectomy.

GALLSTONE ILEUS

Mechanical obstruction resulting from the passage of a large (>2.5 cm) stone into the bowel through a cholecystoduodenal fistula. Obstruction is often at the ileocecal valve.

- ***Hx/PE:*** Classic presentation is a subacute SBO in an older adult female. Patients may have no history of biliary colic.
- ***Dx:*** X-ray of the abdomen with characteristics of SBO and pneumobilia (gas in the biliary tree) confirming diagnosis. Upper GI barium contrast images will demonstrate no contrast in the colon.

- ***Tx:*** Laparotomy with stone extraction; closure of the fistula and cholecystectomy

POSTCHOLECYSTECTOMY SYNDROME

Persistent abdominal pain and dyspepsia in a patient who has had a cholecystectomy. This syndrome may occur immediately after the procedure (early postcholecystectomy syndrome [PCS]) or months afterwards (late PCS). PCS can be caused by several conditions. One-half of patients have biliary, pancreatic, or GI disorders, and the other half have extraintestinal disease.

- **Early PCS causes:** Biliary injury, retained cystic duct, or CBD stones
- **Late PCS causes:** Recurrent CBD stones, bile duct stricture, inflamed cystic duct or gallbladder remnant, papillary stenosis, or biliary dyskinesia (motor forms of sphincter of Oddi dysfunction)
- **Extrabiliary GI causes of PCS:** IBS, pancreatitis, pancreatic tumors, pancreatic divisum, hepatitis, PUD, mesenteric ischemia, diverticulitis, or esophageal diseases
- **Extraintestinal causes of PCS:** Intercostal neuritis, wound neuroma, coronary artery disease (CAD), or psychomotor disorders
- ***Hx/PE:*** Postoperative persistent abdominal pain and dyspepsia
- ***Dx:*** Imaging (eg, ultrasound, CT, or MRCP) to determine underlying cause of PCS (eg recurrent stones, bile duct injury)
- ***Tx:*** Tailored to underlying cause of PCS
- ***Prevention:*** Careful selection of patients who would benefit from cholecystectomy, weighing the risks/benefits of surgery against each in the context of underlying medical conditions and overall stability of the patient

KEY FACT

Bile acid diarrhea may be a part of postcholecystectomy syndrome. With the gallbladder no longer present, excess bile acids can enter the colon and continuous drainage can overcome the terminal ileum’s ability to reabsorb bile, causing diarrhea. Usually resolves on its own. Tx: cholestyramine or colestipol.

BILIARY CYST

- ***Hx/PE:*** Most patients with biliary cysts will present before the age of 10 with the triad of abdominal pain, jaundice, and a palpable mass (not all will have all three in the triad). Other symptoms that may be seen include nausea/vomiting, pain, fever, and jaundice. Others may have cysts discovered incidentally on imaging.
- ***Dx:*** Laboratory evaluation is often normal. If obstruction is present within the biliary system, there may be transaminitis and hyperbilirubinemia.
- ***Prognosis:*** Biliary cysts are associated with an increased risk of cholangiocarcinoma, and surgical resection via Roux-en-Y hepaticojejunostomy may be indicated.

CHOLANGIOCARCINOMA

Arise from squamous cells of the biliary epithelium. It has the potential to be highly lethal due to an insidious presentation. Symptoms typically arise when obstruction ensues from the growing tumor. Cholangiocarcinoma may be extrahepatic or intrahepatic, with intrahepatic cholangiocarcinoma typically presenting even more insidiously (and often incidentally on imaging) than extrahepatic cholangiocarcinoma. Intrahepatic cholangiocarcinoma will be discussed here.

- ***Risk factors:*** Patients may have history of PSC, fibropolycystic liver disease, chronic liver disease, or parasitic exposure to liver flukes.
- ***Hx/PE:*** Cholangiocarcinoma manifests itself with jaundice, pruritis, clay-colored stools, and dark urine. Patients may also have a dull/achy RUQ abdominal pain and weight loss. Laboratory evaluation will typically reveal hyperbilirubinemia, elevated alkaline phosphatase, and either normal or slightly elevated transaminase levels.
- ***Dx:*** Tumor markers (CA 19-9, CEA, α-fetoprotein [AFP]), and abdominal imaging (ultrasound, CT, MRCP) raise suspicion for the diagnosis of cholangiocarcinoma. EUS with fine-needle aspiration (FNA) or ERCP allows for tissue sampling to confirm the diagnosis.
- ***Tx:*** Those with distal cholangiocarcinoma who meet criteria for surgical resection can have surgical resection performed via a pancreaticoduodenectomy (Whipple procedure). Those who have evidence of metastasis may require chemoradiation.

LIVER DISEASE

ABNORMAL LIVER ASSOCIATED ENZYMES

Liver diseases can be divided into several patterns, based on LFT results as follows:

- **Hepatocellular injury:** ↑ aspartate aminotransferase (AST) and alanine aminotransferase (ALT)
- **Cholestasis:** ↑ alkaline phosphatase
- **Mixed:** Combination of hepatocellular and cholestatic picture
- **Isolated hyperbilirubinemia:** ↑ bilirubin

Jaundice is a clinical sign that occurs when bilirubin levels exceed 2.5 mg/dL. Figures 2.6-33 and 2.6-34 summarize the clinical approach toward cholestasis and isolated hyperbilirubinemia.

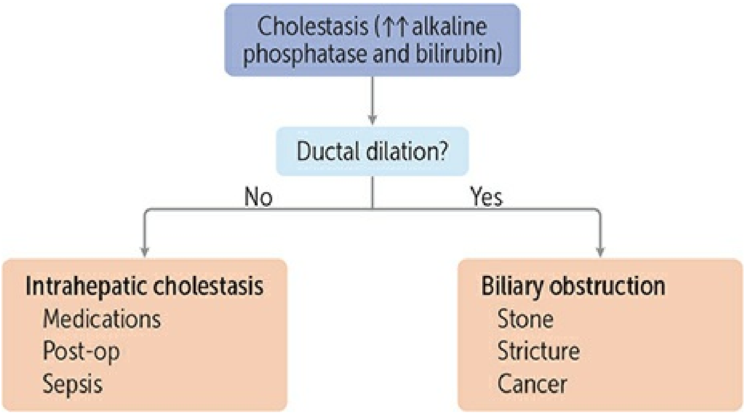


FIGURE 2.6-33. **Approach to cholestasis.** (Reproduced with permission from USMLE-Rx.com.)

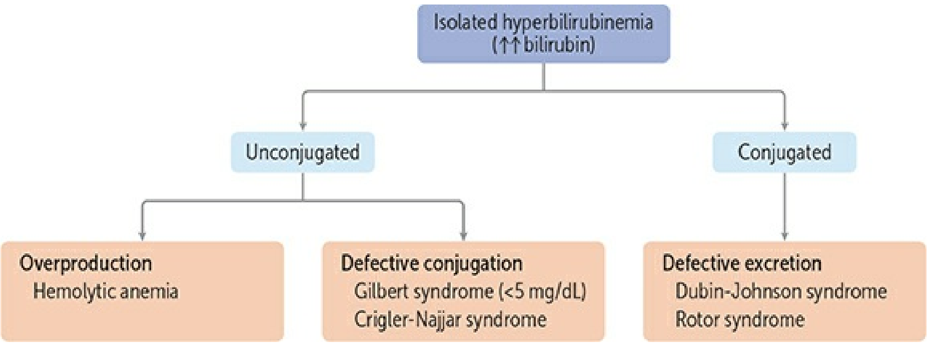

Isolated hyperbilirubinemia (↑↑ bilirubin)
Unconjugated
Conjugated
Overproduction
Hemolytic anemia
Defective conjugation
Gilbert syndrome (<5 mg/dL)
Crigler-Najjar syndrome
Defective excretion
Dubin-Johnson syndrome
Rotor syndrome

FIGURE 2.6-34. **Approach to isolated hyperbilirubinemia.** (Reproduced with permission from USMLE-Rx.com.)

HEPATITIS

Inflammation of the liver leading to cell injury and necrosis. Hepatitis can be either acute or chronic.

- **Acute:** Most common causes are viruses (hepatitis A virus [HAV], hepatitis B virus [HBV], hepatitis C virus [HCV], hepatitis D virus [HDV], hepatitis E virus [HEV]) and drugs (alcohol, acetaminophen, isoniazid [INH], methyldopa).
  - Fulminant: This is also known as acute liver failure. Severe liver injury with international normalized ratio (INR) >1.5 and hepatic encephalopathy in a patient without underlying chronic liver disease.
- **Chronic:** The most common causes are chronic viral infection (HCV most common in United States, HBV worldwide), alcohol, autoimmune hepatitis, and metabolic syndromes (Wilson disease, hemochromatosis, α_1-antitrypsin deficiency).

KEY FACT

Hepatitis **C** virus (H**C**V) is **C**hronic; 70% to 80% of patients with HCV infection will develop chronic hepatitis.

History/PE

- **Acute hepatitis:**
  - Acute hepatitis often begins with a nonspecific viral prodrome (malaise, fever, joint pain, nausea, vomiting, changes in bowel habits) followed by jaundice and RUQ tenderness. Exam often reveals jaundice, scleral icterus, and tender hepatomegaly.
  - HAV and HEV have only a self-limited acute phase; HBV and HCV may feature a mild acute phase or none at all. Acetaminophen toxicity can cause a life-threatening hepatitis. Table 2.6-18 outlines further distinctions among these.

TABLE 2.6-18. **Types of Hepatitis**

VIRUS TYPE	MODE OF TRANSMISSION	PRESENTATION	NOTES
HAV	Fecal-oral	Typically self-limited acute hepatitis May lead to fulminant hepatic failure	Most common cause of acute viral hepatitis worldwide
HBV	Bodily fluids/ blood-borne	May be asymptomatic, but may present as viral prodrome (this is listed above) and/or jaundice May lead to fulminant hepatic failure and require treatment with antivirals or liver transplant in severe cases	<10% of infections in adults become chronic, while most vertically transmitted become chronic Extremely high transmission rate
HCV	Bodily fluids	Asymptomatic or viral prodrome and/or jaundice	80% become chronic Less likely to be sexually transmitted than HBV May present with very mild acute phase Very rarely leads to acute liver failure If palpable purpura, arthralgia, and low complement levels, cryoglobulinemia a possibility
HDV	Bodily fluids	Co-infection with HBV or superinfection in patient with prior HBV (more severe)	Requires HBV surface antigen. H**D**V is **D**ependent on HBV
HEV	Fecal-oral	Typically self-limited acute hepatitis similar to HAV	High mortality rate in pregnant women May become chronic in patients with immunosuppression

- **Chronic hepatitis:** It may be asymptomatic, or it may cause fatigue and joint and muscle pains. Jaundice and complications of portal hypertension typically occur only when the disease progresses to cirrhosis. At least 80% of those infected with HCV and 10% of those with HBV in adulthood will develop persistent infection with chronic active hepatitis.

MNEMONIC

Hepatitis virus—

A: Acute (up to 2 months of nausea/vomiting, jaundice, fatigue, fever, abdominal pain)
B: Body fluids (blood, sexual activity, vertical transmission, breastfeeding)
C: Chronic (becomes chronic for most)
D: Double whammy (coinfection of hepatitis B required)
E: Expecting (pregnant patients)

Q

A 21-year-old college student in the midst of final exams presents to a local clinic with “yellow eyes.” His physical exam is unremarkable except for scleral icterus, and a CBC and blood smear show no abnormalities. A comprehensive metabolic profile reveals a normal AST and ALT but elevated unconjugated bilirubin. What is the most likely diagnosis?

Diagnosis

- **Acute hepatitis:** Labs reveal markedly ↑ ALT and AST, ↑ gamma-glutamyl transferase (GGT), ↑ ferritin, and ↑ bilirubin/alkaline phosphatase.
- **Chronic hepatitis:** ALT and AST are either mildly elevated or even normal/low for >3 to 6 months, contrasting with the marked elevations of acute hepatitis.

- Diagnosis of viral hepatitis is made by hepatitis serology (see Table 2.6-19 and Fig. 2.6-35 for a description and timing of serologic markers). The physician may require a liver biopsy if diagnosis is uncertain or to rule out other causes of liver disease in chronic or severe cases.

TABLE 2.6-19. Key Hepatitis Serologic Markers

SEROLOGIC MARKER	DESCRIPTION
IgM HAVAb	IgM antibody to HAV; the best test to detect acute HAV
HBsAg	Antigen found on the surface of HBV; continued presence indicates carrier state
HBsAb	Antibody to HBsAg; indicates immunity to HBV
HBcAb	Antibody to HBcAg; IgM ⊕ during the window period IgG HBcAb is an indicator of prior or current infection
H**Be**Ag	A different antigenic determinant in the HBV core An important indicator of transmissibility (**Be**ware!)
HBeAb	Antibody to e antigen; indicates low transmissibility

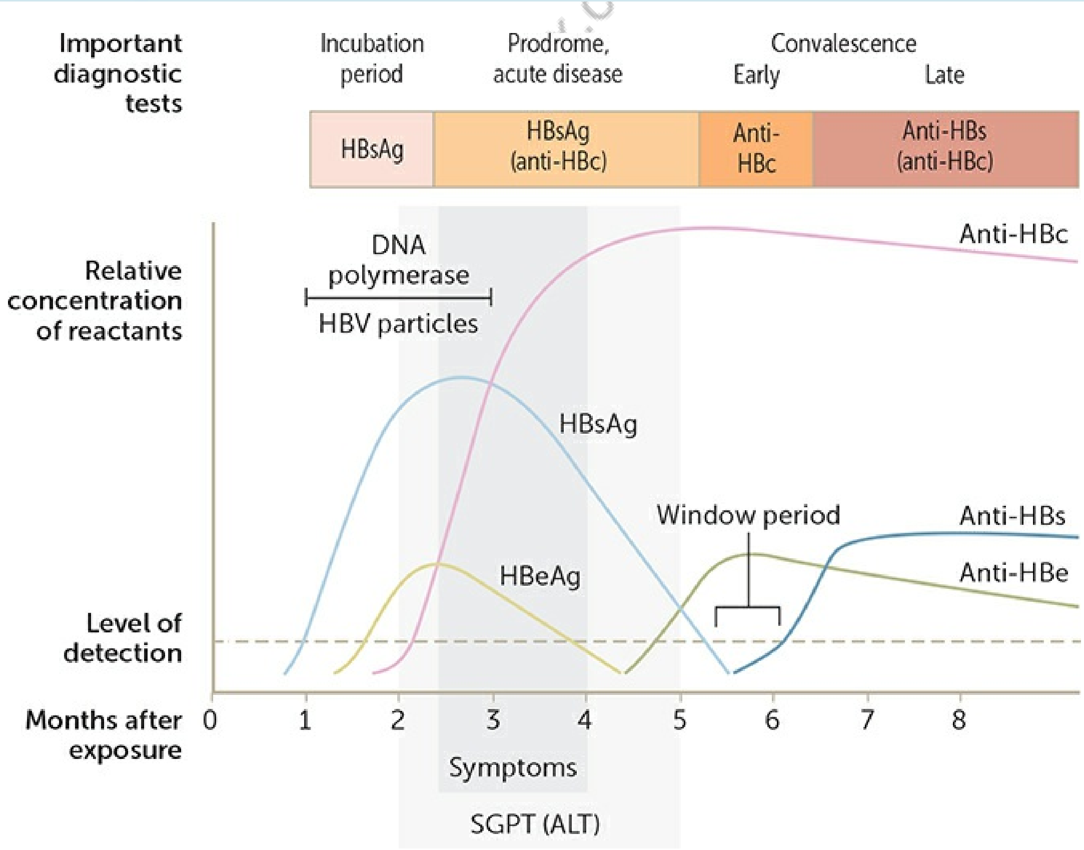


FIGURE 2.6-35. Time course of hepatitis B with serologic markers. (Reproduced with permission from USMLE-Rx.com.)

- **Other diagnostic studies include the following:**

- **Autoimmune hepatitis:** ⊕ Anti–nuclear and anti–smooth muscle antibodies (type 1) and anti–liver-kidney microsomal-1 antibodies and anti–liver cytosol antibodies (type 2). May also present with elevated serum gamma globulins (IgG) and perinuclear antineutrophil cytoplasmic antibody (p-ANCA).
- **Hemochromatosis:** ↑ ferritin and transferrin saturation >50%. Liver biopsy showing high hepatic iron index.
- **Wilson disease:** ↓ ceruloplasmin, ↑ urine copper, Kayser-Fleischer rings. Liver biopsy if diagnosis uncertain.

MNEMONIC

An **AST**/ALT ratio >2 suggests alcohol hepatitis: you're **T**oasted.

A

The most likely diagnosis is Gilbert syndrome, an autosomal recessive disorder of bilirubin glucuronidation caused by ↓ activity of the enzyme glucuronyl transferase. Patients present with unconjugated hyperbilirubinemia but have a normal CBC, blood smear, and LFTs. The condition is benign, and no treatment is indicated.

Treatment

- **Acute hepatitis:** Generally supportive care. Possibility of acute HBV requiring treatment with antivirals.
- **Alcoholic hepatitis:** Treatment of alcohol withdrawal with benzodiazepines if showing signs of withdrawal, providing adequate hydration and supplementation to maintain nutritional status.
- **Drug-induced hepatitis:** General treatment—removal of offending agent with exceptions, including use of *N*-acetylcysteine for acetaminophen overdose and l-carnitine in the treatment of valproic acid overdose.
- **Chronic hepatitis:** Etiology-specific treatment.
- **Chronic HBV infection:** Tenofovir and entecavir most commonly used, as they have the highest barrier to resistance. Other agents, including telbivudine, adefovir, and lamivudine, are not recommended because of a high rate of resistance.
- **Chronic HCV infection:** Varying medications and treatment duration, based on genotype, cirrhosis status, and history of prior treatment. Typically, either two direct-acting antivirals (DAAs) or one DAA plus ribavirin. Interferon is no longer used. This field is rapidly evolving.
- **Most definitive treatment:** Liver transplantation for patients with end-stage liver failure. Emergent transplantation indicated in cases of fulminant hepatic failure.

KEY FACT

Hepatitis B postexposure prophylaxis: Nonimmunized individuals require both vaccination and immunoglobulins. Hepatitis B–immunized individuals and those exposed to hepatitis C do not require any postexposure prophylaxis.

KEY FACT

The sequelae of chronic hepatitis include cirrhosis, portal hypertension, liver failure, and hepatocellular carcinoma.

Complications

Cirrhosis, liver failure, hepatocellular carcinoma (3%–5%).

CIRRHOSIS

Generally speaking, cirrhosis is progressive fibrosis of liver parenchyma causing pathologic dysfunction resulting from chronic injury, which may arise by various means.

- Pathophysiology involves bridging fibrosis and nodular regeneration resulting from chronic hepatic injury.
- Most common etiologies in the United States are alcohol, chronic HCV, and nonalcoholic steatohepatitis. Cirrhosis occurs in a progressive pattern, starting at a normal liver and eventually resulting in liver cirrhosis (see Fig. 2.6-36 for progression and Fig. 2.6-37 for a visual representation). Etiologies can be as follows:

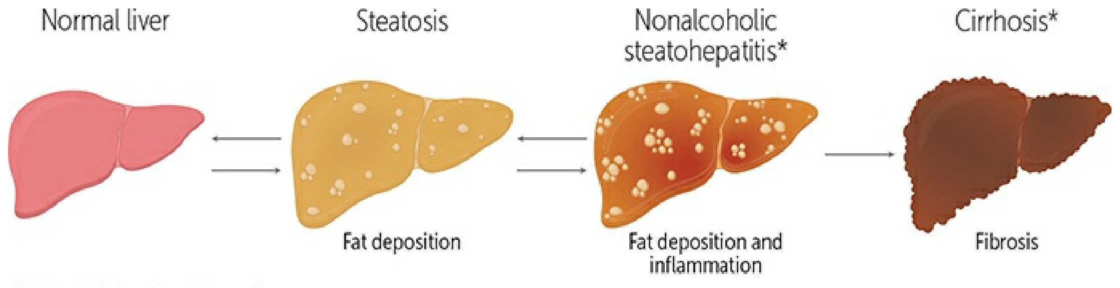

Normal liver
Steatosis
Nonalcoholic steatohepatitis*
Cirrhosis*
Fat deposition
Fat deposition and inflammation
Fibrosis
*Risk factor for hepatocellular carcinoma

FIGURE 2.6-36. **Liver cirrhosis progression.** (Reproduced with permission from USMLE-Rx.com.)

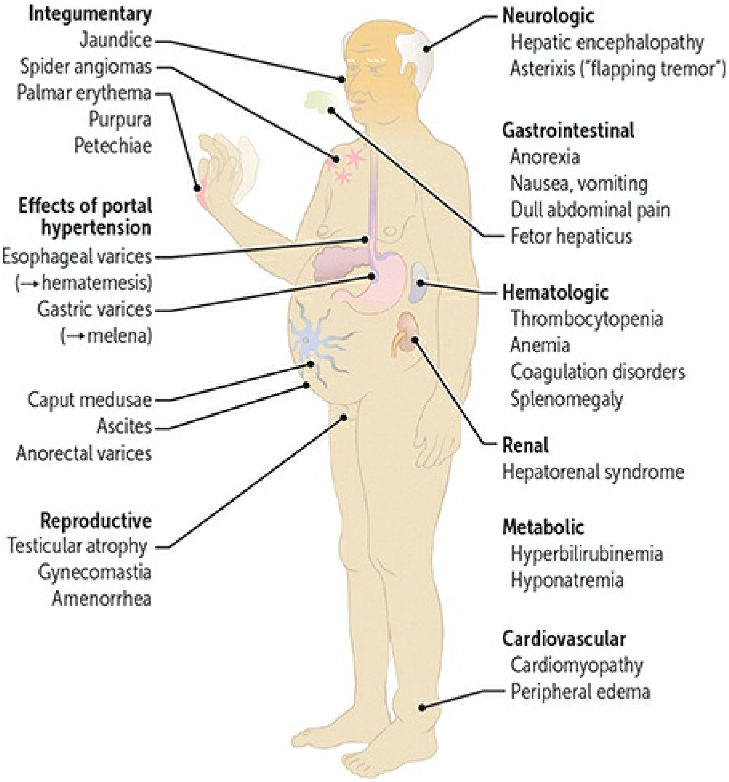

Integumentary
Jaundice
Spider angiomas
Palmar erythema
Purpura
Petechiae
Effects of portal hypertension
Esophageal varices (→hematemesis)
Gastric varices (→melena)
Caput medusae
Ascites
Anorectal varices
Reproductive
Testicular atrophy
Gynecomastia
Amenorrhea
Neurologic
Hepatic encephalopathy
Asterixis ("flapping tremor")
Gastrointestinal
Anorexia
Nausea, vomiting
Dull abdominal pain
Fetor hepaticus
Hematologic
Thrombocytopenia
Anemia
Coagulation disorders
Splenomegaly
Renal
Hepatorenal syndrome
Metabolic
Hyperbilirubinemia
Hyponatremia
Cardiovascular
Cardiomyopathy
Peripheral edema

FIGURE 2.2-37. **Presentation of cirrhosis/portal hypertension.** (Reproduced with permission from USMLE-Rx.com.)

- Etiology of all causes of chronic hepatitis: Biliary tract disease (primary biliary cirrhosis, PSC); posthepatic causes, including right-sided heart failure, constrictive pericarditis, and Budd-Chiari syndrome (hepatic vein thrombosis secondary to hypercoagulability).

History/PE

- May be asymptomatic, though may present with jaundice, easy bruising (coagulopathy), and complications of portal hypertension such as ascites, hepatic encephalopathy (asterixis, altered mental status; see Table 2.6-20 for hepatic encephalopathy grading), gastroesophageal varices, hepatic hydrothorax (transudative pleural effusion), and thrombocytopenia. Ascites can be complicated by spontaneous bacterial peritonitis. Tables 2.6-21 and 2.6-22 help differentiate ascitic fluid characteristics and their associated differential diagnoses.

TABLE 2.6-20. **Grading of Encephalopathy by West Haven Criteria**

GRADE	MENTAL STATUS	ASTERIXIS	ELECTROENCEPHALOGRAPHY (EEG)
I	▪ Euphoria/depression ▪ Mild confusion ▪ Slurred speech ▪ Disordered sleep	Possible	Usually normal
II	▪ Lethargy ▪ Moderate confusion	Yes	Abnormal
III	▪ Marked confusion ▪ Incoherent ▪ Sleeping but arousable	Yes	Abnormal
IV	▪ Coma	No	Abnormal

TABLE 2.6-21. Etiologies of Ascites by SAAG

SAAG > 1.1	SAAG < 1.1
Related to portal hypertension: ▪ Presinusoidal: Splenic or portal vein thrombosis, schistosomiasis ▪ Sinusoidal: Cirrhosis ▪ Postsinusoidal: Right heart failure, constrictive pericarditis, Budd-Chiari syndrome	Not related to portal hypertension: ▪ Nephrotic syndrome ▪ TB ▪ Malignancy with peritoneal carcinomatosis (eg, ovarian cancer)

TABLE 2.6-22. Ascites Fluid Characteristics

Color	▪ **Bloody:** trauma, malignancy, TB (rare) ▪ **Milky:** chylous ▪ **Turbid:** possible infection ▪ **Straw-colored:** likely more benign causes
Neutrophils	▪ ≥250/mm^3: peritonitis (secondary or spontaneous bacterial)

Total Protein	▪ ≥2.5 g/dL (high-protein ascites)
	  ▪ CHF, constrictive pericarditis, peritoneal carcinomatosis, TB, Budd-Chiari syndrome, fungal
	▪ <2.5 g/dL (low-protein ascites)
	  ▪ Cirrhosis, nephrotic syndrome

SAAG	▪ ≥1.1 g/dL (indicates portal hypertension) ▪ Cardiac ascites, cirrhosis, Budd-Chiari syndrome ▪ <1.1 g/dL (absence of portal hypertension) ▪ TB, peritoneal carcinomatosis, pancreatic ascites, nephrotic syndrome

- May reveal an enlarged, palpable, or firm liver and other signs of portal hypertension and liver failure (Fig. 2.6-37).

KEY FACT

Spontaneous bacterial peritonitis is a common complication in patients with cirrhosis and ascites, and if they present with signs and symptoms suggestive of infection, paracentesis should be performed. Spontaneous bacterial peritonitis is diagnosed by >250 polymorphonuclear leukocytes (PMNs)/mm^3 in the ascitic fluid.

Diagnosis

- **Most accurate diagnostic test:** Liver biopsy showing bridging fibrosis and nodular regeneration
- **Alternative diagnostic tests:** Biochemical (eg, AST:ALT ratio, APRI, FIB-4, thrombocytopenia, other proprietary tests [fibroscan, fibrosure]), and elastographic measures of fibrosis (fibroscan, MR elastography, US elastography).
- **Synthetic dysfunction:** ↓ albumin, ↑ prothrombin time (PT)/INR, and ↑ bilirubin
- **Portal hypertension:** Thrombocytopenia (secondary to hypersplenism, sequestration of platelets in the liver, and ↓ thrombopoietin production), varices, ascites (paracentesis)
- **Etiology:** Hepatitis serologies, autoimmune markers, serum ferritin, ceruloplasmin, and α_1-antitrypsin
- If ascites present, etiology of ascites determined by the serum-ascites albumin gradient (SAAG = serum albumin–ascites albumin); see Table 2.6-20

Treatment

The goal is to treat and prevent the progression of cirrhosis and minimize factors that can lead to decompensation (see Table 2.6-23). All cirrhotic patients should receive vaccinations for hepatitis A, hepatitis B, and PPSV-23 (pneumonia).

TABLE 2.6-23. Complications of Cirrhosis

COMPLICATION	MECHANISM/HISTORY	MANAGEMENT
Ascites	↑ portal hypertension results in transudative effusion Physical exam reveals abdominal distention, fluid wave, and shifting dullness to percussion	Sodium restriction and diuretics (furosemide, spironolactone); large-volume paracentesis. **TIPS** (**T**ransjugular **I**ntrahepatic **P**or**t**o**s**ystemic **S**hunt) Treat underlying liver disease if possible
Spontaneous bacterial peritonitis	Presents with fever, abdominal pain, chills, nausea, and vomiting Treatment indicated if diagnostic paracentesis reveals >250 PMNs/mL	IV antibiotics acutely (third-generation cephalosporin), IV albumin; prophylaxis with a fluoroquinolone to prevent recurrence Development of SBP is associated with poor 1-year prognosis
Hepatorenal syndrome	Prerenal failure in the setting of severe liver disease A diagnosis of exclusion Caused by splanchnic vasodilation and decreased blood flow to the kidneys Urinary sodium <10 mEq/L "Healthy kidneys in an unhealthy environment"	Initially trial of volume repletion and rule out other causes of renal failure May use octreotide (decrease splanchnic vasodilation) and midodrine (increase blood pressure) May require dialysis Poor prognosis Liver transplantation can be curative
Hepatic encephalopathy	↓ clearance of ammonia; often precipitated by dehydration, infection, electrolyte abnormalities, and GI bleeding	Lactulose and/or rifaximin Correct underlying triggers
Esophageal varices	Portal hypertension leads to ↑ flow through portosystemic anastomoses	Endoscopic surveillance in all patients with cirrhosis; medical prophylaxis with nonselective β-blockers or endoscopic band ligation to prevent bleeding in patients with known varices For acute bleeding, endoscopy with band ligation or sclerotherapy is indicated. Urgent TIPS in refractory cases (associated with high mortality)
Coagulopathy	Impaired synthesis of all clotting factors (except VIII)	For acute bleeding, administer fresh frozen plasma Vitamin K will not correct coagulopathy

CHF, Congestive heart failure; *SAAG*, serum ascites albumin gradient; *SBP*, spontaneous bacterial peritonitis; *TB*, tuberculosis.

KEY FACT

Hepatic encephalopathy manifestations range from changes in behavior to coma. Hepatic encephalopathy is graded, based on degree of symptomatology. Asterixis may be present.

SPONTANEOUS BACTERIAL PERITONITIS

Spontaneous bacterial peritonitis (SBP) is defined as an infection of the ascitic fluid, typically presenting in patients with advanced cirrhosis. The higher the Model for End-stage Liver Disease (MELD) score, the higher the risk of SBP.

KEY FACT

Common causes of SBP include perforation peritonitis (eg, perforated peptic ulcer), nonperforation peritonitis (eg, perinephric abscess), or translocation of GI flora.

History/PE

- SBP classically presents with fever, abdominal pain, chills, nausea, altered mental status, and vomiting.

- Patients may be asymptomatic (~13%–30% of patients have no signs or symptoms).
- Altered mental status is seen in approximately one-half of patients and does not correlate with ammonia levels.
- Lab abnormalities may include subtle leukocytosis, metabolic acidosis, and azotemia.

Etiologies

Most common cause is *Escherichia coli*. Other organisms include *Klebsiella pneumonia*, *Streptococcus pneumonia*, *Enterobacteriaceae*, and *Staphylococcus*.

Pathogenesis

- Disturbance in gut flora is related to overgrowth and extraintestinal translocation.
- It is thought cirrhosis predisposes to a bacterial overgrowth because of altered small intestinal motility.
- Bacterial seeding is secondary to urinary tract infections, pneumococcal sepsis, cellulitis, pharyngitis, and dental infections.

Risk Factors

- Advanced cirrhosis
- Previous episode of SBP
- Variceal hemorrhage
- Total protein concentration <1g/dL in ascites fluid
- Serum total bilirubin >2.5 mg/dL
- GI bleed
- Use of PPIs

Diagnosis

- Paracentesis of ascitic fluid with analysis of cell count. Samples should be taken before antibiotic administration.
- Ascitic, blood, and urine cultures indicated.
- Elevated ascitic fluid absolute PMN count (>250 PMNs/mm^3) is diagnostic.
- Evaluation needed for secondary causes of peritonitis.

Treatment

- IV antibiotics (third-generation cephalosporin)
- IV albumin for patients with renal dysfunction
- Prophylaxis with a trimethoprim-sulfamethoxazole or a fluoroquinolone to prevent recurrence

KEY FACT

SBP prophylaxis is important in all cirrhotic patients admitted for a GI bleed/variceal hemorrhage due to the increased risk of bacterial translocation.

Prognosis

- Development of SBP is associated with poor 1-year prognosis due to its association with advanced cirrhosis

- Recurrence rates of SBP are close to 70%

ISCHEMIC HEPATITIS

Also called shock liver, hypoxic hepatitis, and hypoxic liver injury. Generally is diffuse hepatic injury resulting from acute hypoperfusion.

- ***Risk factors:*** Any type of shock.
- ***Hx/PE:*** History of shock (any kind of shock) or other acute causes of blood supply interruption (eg, hepatic sickle cell crisis or hepatic artery thrombosis in those who have undergone liver transplantation or who have pre-existing portal vein thrombosis).
- ***Dx:*** History of hypotensive episode followed by transaminitis with LFTs 25 to 250 times the normal levels (usually with AST and ALT >1000 units/L) and a massive rise in lactate dehydrogenase (LDH).
- ***Tx:*** Addressing underlying causes of ischemic insult.
- ***Prognosis:*** In the absence of continued ischemic insult, LFTs usually normalize in 7 to 10 days. The mortality rates are around 25% in ischemic hepatitis with shock (although mortality is mostly due to underlying cause of shock rather than hepatitis alone). Occasionally patients will progress to acute liver failure, where mortality rates range from 60% to 100%.

KEY FACT

There are few causes of liver injury that cause LFTs to rise above 1000 units/L. These include drug-induced hepatitis, viral hepatitis, and ischemic hepatitis.

ACUTE LIVER FAILURE

Also called fulminant hepatic failure, acute hepatic necrosis, fulminant hepatic necrosis, and fulminant hepatitis. Characterized by severe acute liver injury, hepatic encephalopathy, and an elevated PT/INR (≥1.5) that develops in less than 26 weeks (versus chronic liver failure). The diagnosis may also be made in those with newly discovered Wilson disease, reactivation of chronic hepatitis B, or autoimmune hepatitis recognized in less than 26 weeks who also have cirrhosis.

- ***Etiology:*** Many different etiologies, the most common of which are due to drug-induced and viral hepatitis
- ***Hx/PE:*** Fatigue/malaise, lethargy, anorexia, nausea/vomiting, RUQ pain, pruritis, jaundice, abdominal distention (secondary to ascites), and hepatic encephalopathy
- ***Dx:*** Must have elevated transaminases, hepatic encephalopathy (any grade), and prolonged PT (INR ≥1.5)
- ***Tx:*** Diagnosing and treating the underlying cause of acute liver failure, transferring to ICU at a liver transplant center whenever possible, avoiding hepatotoxic medications, and addressing complications that can occur
- ***Complications:*** Hemodynamic derangement, bleeding, malnutrition, electrolyte derangements (hypokalemia, hyponatremia, hypophosphatemia, and hypoglycemia), hepatic encephalopathy, cerebral edema with associated increased intracranial pressure elevation, seizures, acute renal failure, and pulmonary edema/infections

KEY FACT

Those with acute severe alcoholic hepatitis, even if recognized in less than 26 weeks, are considered to have acute-on-chronic severe alcoholic hepatitis as opposed to acute liver failure, since there is usually a long history of alcohol use disorder.

HEPATORENAL SYNDROME

Acute kidney injury caused by acute or chronic liver disease causing fulminant renal failure.

- ***Pathogenesis:*** Arterial vasodilation in the splanchnic circulation (arteries supplying visceral organs of the abdomen) secondary to portal hypertension–induced nitric oxide release. This is ultimately unable to be overcome by the renin-angiotensin-aldosterone system (RAAS), leading to kidney injury.
- ***Hx/PE:*** Underlying liver disease accompanied by a progressive rise in serum creatinine.
  - **Type 1:** More serious; at least a twofold increase in serum creatinine to a level greater than 2.5 mg/dL in less than 2 weeks.
  - **Type 2:** Kidney failure that is less severe than type 1 hepatorenal syndrome. The major clinical feature of type 2 hepatorenal syndrome is ascites resistant to diuretics.
- ***Dx:*** One of exclusion, meaning other causes of potential kidney injury must be ruled out.
- ***Tx:*** Addressing underlying liver pathology and treating appropriately (if possible) in addition to medical therapy/optimization. Those who do not respond may benefit from a TIPS procedure.

HEPATOPULMONARY SYNDROME

Hypoxemia secondary to ventilation/perfusion mismatch caused by acute or chronic liver disease.

- ***Pathogenesis:*** As with hepatorenal syndrome, this is thought to be due to increased nitric oxide release due to portal hypertension. This results in dilation of pulmonary vasculature, leading to increased blood delivery to pulmonary circulation without an equal increase in ventilation. This results in blood being delivered to the left side of the heart that is inadequately oxygenated
- ***Hx/PE:*** Underlying liver disease in addition to dyspnea (nonspecific), platypnea (increased dyspnea while standing; relieved while recumbent), orthodeoxia (decreased oxygen saturation when moving from recumbent to standing position), and hypoxemia.
- ***Dx:*** One of exclusion, meaning other causes of hypoxemia and dyspnea should be ruled out. In general, those with underlying liver disease with impaired oxygenation (A-a gradient >20 mm Hg, PaO_2 <70 mm Hg, and identified pulmonary vascular abnormalities identified on transthoracic contrast echocardiography.
- ***Tx:*** Observation with pulse oximetry or arterial blood gases every 6 to 12 months is adequate to monitor for worsening disease process; supplemental oxygen may be required if symptomatic. In those with severe to very severe disease, in addition to oxygen supplementation liver transplantation should be considered as well as TIPS. Liver transplantation is curative.

HEPATIC HYDROTHORAX

Generally speaking, hepatic hydrothorax is accumulation of ascitic fluid in the pleural cavity in patients with underlying liver disease.

- ***Pathogenesis:*** Thought to be due to passage of ascitic fluid from the peritoneal cavity through diaphragm defects into the pleural cavity. Defects are usually <1 cm and associated with the tendinous portion of the diaphragm. Most often, hepatic hydrothorax occurs on the right side of the diaphragm due to the left side being more muscular and thicker.
- ***Hx/PE:*** Typically presents with dyspnea (nonspecific), a nonproductive cough, pleuritic chest pain, and hypoxemia in a patient with underlying liver disease and ascites.
- ***Dx:*** Identification of a pleural effusion on CXR and ruling out other causes of pleural effusion. Further evaluation via a thoracentesis with fluid studies revealing transudative fluid can be performed to further rule out other potential causes of plural effusion. Similar to evaluating SAAG in ascitic fluid, evaluating the serum-pleural albumin gradient should reveal a gradient of >1.1 g/dL because the fluid is ascitic fluid.
- ***Tx:*** Similar to the treatment of ascites (sodium restriction and diuretics.) Additionally, therapeutic thoracentesis can be performed for symptom relief. In those with refractory hepatic hydrothorax, a TIPS procedure can be considered. In those who are not good candidates for TIPS, pleurodesis (chemical or mechanical obliteration of the pleural space to prevent accumulation of fluid/air), surgical repair of diaphragm defects, and liver transplantation may be considered.

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT PROCEDURE

Creates a low-resistance channel between the portal circulation and systemic circulation to reduce portal pressure and help treat sequalae of portal hypertension (eg, ascites, varices.) Generally speaking, this minimally invasive procedure is performed under fluoroscopic guidance in an interventional radiology suite, using wires and catheters to ultimately place a stent connecting a hepatic vein to a portal vein.

- **Indications:** Bleeding related to portal hypertension (eg, esophageal, gastric, or ectopic varices), portal hypertensive gastropathy/intestineopathy, Budd-Chiari syndrome, hepatorenal syndrome, hepatopulmonary syndrome, hepatic hydrothorax, and refractory ascites
- **Absolute contraindications:** Congestive heart failure (CHF), severe tricuspid regurgitation, severe pulmonary hypertension, polycystic liver disease, active systemic infection/sepsis, and unrelieved biliary obstruction
- **Postprocedural complications:** Hepatic encephalopathy (secondary to increased ammonia in circulation; typically managed with rifaximin or lactulose), recurrent bleeding due to shunt stenosis/thrombosis (typically managed with angioplasty), and heart failure due to increased preload.

KEY FACT

Hepatopulmonary syndrome in portal hypertension may be from ↑ nitric oxide production → ↑ pulmonary vascular dilation and V/Q mismatch. Blood that flows through the pulmonary vasculature does not receive proper oxygenation due to an unchanged amount of ventilation from the lungs.

PRIMARY SCLEROSING CHOLANGITIS

An idiopathic disorder characterized by progressive inflammation and fibrosis accompanied by strictures of extrahepatic and intrahepatic bile ducts. The disease usually presents in young males with ulcerative colitis. Patients are at increased risk for cholangiocarcinoma.

History/PE

Presents with progressive jaundice, pruritus, and fatigue.

Diagnosis

- Laboratory findings including ↑ ALP and ↑ bilirubin; PSC also associated with p-ANCA antibodies
- **Most accurate test:** MRCP/ERCP showing multiple bile duct strictures and dilatations (“beading”). MRCP is preferred initially as it is noninvasive.
- Liver biopsy revealing periductal sclerosis (“onion skinning”)
- Colonoscopy for all newly diagnosed patients to evaluate for IBD

Treatment

ERCP with dilation and stenting of strictures. Liver transplantation is the definitive treatment. Ursodeoxycholic acid has been shown to improve the liver function profile in some patients.

KEY FACT

Primary sclerosing cholangitis is strongly associated with ulcerative colitis.

PRIMARY BILIARY CHOLANGITIS

Autoimmune disorder characterized by destruction of intrahepatic bile ducts. Most commonly presents in middle-aged females with other autoimmune conditions.

- ***Hx/PE:*** Presents with progressive jaundice, pruritus, and fat-soluble vitamin deficiencies (A, D, E, K)
- ***Dx:*** Laboratory findings including ↑ ALP, ⊕ antimitochondrial antibody, and ↑ cholesterol
- ***Tx:*** Ursodeoxycholic acid (slows progression of disease) or obeticholic acid for those intolerant of or unresponsive to ursodeoxycholic acid; cholestyramine for pruritus; liver transplantation

KEY FACT

Primary biliary cholangitis is an autoimmune disease that presents with jaundice and pruritus in middle-aged females.

NONALCOHOLIC FATTY LIVER DISEASE

Steatosis of hepatocytes leading to liver injury. Some patients progress to nonalcoholic steatohepatitis (NASH) and are at risk for liver fibrosis and cirrhosis. It is associated with insulin resistance and metabolic syndrome.

- ***Dx:*** Largely a diagnosis of exclusion. Liver biopsy may show steatosis or steatohepatitis.
- ***Tx:*** Weight loss, diet, and exercise. If NASH is present, the physician should consider

vitamin E and pioglitazone.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma is one of the most common cancers worldwide despite its relatively low incidence in the United States. Metastatic disease (especially from colon cancer) is much more common than primary hepatic cancer.

Risk factors: In the United States, risk factors are cirrhosis (from alcohol, HCV, and NASH) and chronic hepatitis B (even without cirrhosis). In developing countries, HBV infection and aflatoxins (in various food sources) are major risk factors.

History/PE

- Patients commonly present with RUQ tenderness, abdominal distention, and signs of chronic liver disease such as jaundice, easy bruising, and coagulopathy. The disease may present as decompensation of previously compensated cirrhosis.
- Exam may reveal tender hepatomegaly.

Diagnosis

Hepatocellular carcinoma is often suggested by the presence of a mass on ultrasound or CT, as well as by abnormal LFTs and significantly elevated AFP levels. Biopsy is required if diagnosis is uncertain, but can be deferred if imaging findings are highly suggestive of hepatocellular cancer.

Treatment

- **Surgical:** Partial hepatectomy if technically feasible and synthetic function preserved. An orthotopic liver transplantation in patients with cirrhosis is preferred treatment if there are only a few small tumors (Milan criteria: single lesion <5 cm or three lesions <3 cm).
- **Nonsurgical:** Transarterial chemoembolization (TACE) and/or radiofrequency ablation. Tyrosine kinase inhibitors (eg, levatinib), immunotherapy (eg, atezolizumab), and anti-VEGF antibodies (eg, bevacizumab) may be indicated for advance metastatic disease.
- May monitor AFP levels (if previously elevated) and use serial surveillance imaging (ultrasound, CT) to screen for recurrence.

KEY FACT

Hepatic adenomas (caused by oral contraceptives) are benign tumors and do not transform into malignancy.

HEMOCHROMATOSIS

A state of iron overload in which hemosiderin accumulates in the liver, pancreas (islet cells), heart, adrenal glands, and pituitary gland

- **Primary hemochromatosis:** An autosomal recessive disease characterized by mutations in the HFE gene that result in excessive absorption of dietary iron
- **Secondary hemochromatosis:** Occurs in patients receiving chronic transfusion therapy (eg, sickle cell disease or α-thalassemia)

History/PE

- Presentation with abdominal pain, DM, hypogonadotropic hypogonadism (due to deposition of hemosiderin in the pituitary), arthropathy of the metacarpophalangeal joints, heart failure, impotence, or cirrhosis.
- Bronze skin pigmentation, cardiac dysfunction (CHF), hepatomegaly, and testicular atrophy. Labs may reveal evidence of DM.
- Lung, kidney, or eye unaffected.

Diagnosis

- **Best initial tests:** Iron studies showing ↑ serum iron, percent saturation of iron, and ferritin with ↓ serum transferrin. A transferrin saturation (serum iron divided by total iron-binding capacity [TIBC]) >45% is highly suggestive of iron overload.
- **Most accurate tests:** *HFE* gene mutation screen (C282Y/H63D) and MRI; liver biopsy (most accurate test) to determine hepatic iron index.

Treatment

- Weekly phlebotomy to normalize serum iron levels (target ferritin between 50 and 100 mcg/L) and then maintenance phlebotomy every 2 to 4 months
- Iron-chelating agents such as deferoxamine, deferiprone, or deferasirox for maintenance therapy

Complications

Cirrhosis, hepatocellular carcinoma, restrictive cardiomyopathy, arrhythmias, DM, impotence, arthropathy, and hypopituitarism. Patients with hemochromatosis (and all patients with cirrhosis) have increased susceptibility to *Vibrio vulnificus*, *Listeria monocytogenes*, and *Yersinia enterocolitica* infections.

WILSON DISEASE (HEPATOLENTICULAR DEGENERATION)

An autosomal recessive disorder that results in defective copper transport and subsequent accumulation and deposition of copper in the liver and brain. Usually occurs in patients <30 years of age.

History/PE

- Presentation with hepatitis/cirrhosis, neurologic dysfunction (ataxia, tremor), and psychiatric abnormalities (psychosis, anxiety, mania, depression)
- May reveal Kayser-Fleischer rings (green-to-brown copper deposits in the Descemet membrane; see Fig. 2.6-38), as well as jaundice, hepatomegaly, asterixis, choreiform movements, and rigidity

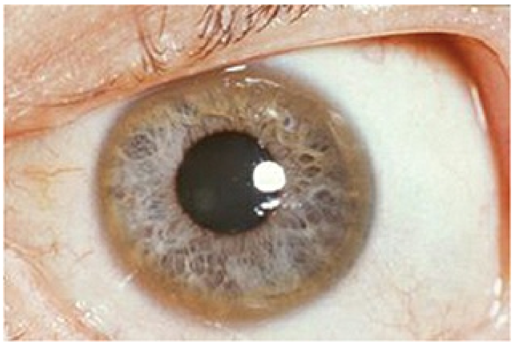


FIGURE 2.6-38. Kayser-Fleischer ring. Note the brown ring encircling the iris. This is a result of copper deposits in the Descemet membrane and is a classic finding in Wilson disease. (Reproduced with permission from van Dijk HA, Fred HL. Images of memorable cases: case 81. Connexions Web site. December 3, 2008. Available at https://cnx.org/contents/KD3uzS6O@3/Images-of-Memorable-Cases-Case-9)

Diagnosis

- **Best initial test:** Serum ceruloplasmin level is decreased.
- If ceruloplasmin level is low, then 24-hour urinary copper excretion (increased) and slit lamp exam (for Keyser-Fleischer rings) are done.
- **Most accurate test:** Liver biopsy with dry copper weight or ATP7B gene testing.

Treatment

Penicillamine or trientine (copper chelators that ↑ urinary copper excretion), dietary copper restriction (avoid shellfish, liver, legumes), and zinc (↑ fecal excretion)

Q

A 36-year-old woman with a past medical history of hypercholesterolemia and type 2 DM presents with intermittent dull RUQ discomfort. The patient does not drink alcohol. Her physical exam is unremarkable. Lab studies show elevated AST and ALT but are otherwise normal. Hepatitis serologies are ⊖. What is the most likely diagnosis?

LIVER TRANSPLANTATION

Indications:

- Acute liver failure
- Cirrhosis with portal hypertension or compromised hepatic function (eg, variceal hemorrhage, ascites, encephalopathy, and hepatorenal syndrome)
- Primary liver neoplasms (hepatocellular carcinoma) that meet specific criteria:
  - Single lesion ≤5 cm
  - Up to three separate lesions ≤3 cm
  - No evidence of gross vascular invasion
  - No regional or nodal metastasis
- Metabolic disorders (eg, Wilson disease, α-1 antitrypsin deficiency, certain glycogen storage diseases, hemochromatosis, acute intermittent porphyria)

Contraindications:

- Uncorrectable cardiopulmonary disease
- Malignancy outside of liver not meeting oncologic criteria for cure

- Hepatocellular carcinoma with metastatic spread
- Intrahepatic cholangiocarcinoma
- Hemangiosarcoma
- Certain anatomic abnormalities
- Uncontrolled sepsis
- Acute liver failure with sustained intracranial pressure >50 mm Hg or cerebral perfusion pressure <40 mm Hg
- Persistent nonadherence to medical care or lack of adequate social support

BENIGN LIVER LESIONS

Focal Nodular Hyperplasia

Solitary liver lesion seen in females. Focal nodular hyperplasia (FNH) is the second most common benign liver lesion. It typically occurs in response to a dystrophic artery, arteriovenous shunting, or congenital vascular malformation. Fibrosis develops in the center of the lesion, creating the characteristic stellate central scar surrounded peripherally by hyperplastic hepatocytes.

- ***Hx/PE:*** Usually asymptomatic and found incidentally on imaging. Those with symptoms tend to have nonspecific abdominal pain, but this is less common.
- ***Dx:*** Seen on contrast-enhanced imaging as a peripherally enhancing lesion on arterial phase with characteristic central stellate appearance. On portal phase imaging, washout is visualized (see Fig. 2.6-39).

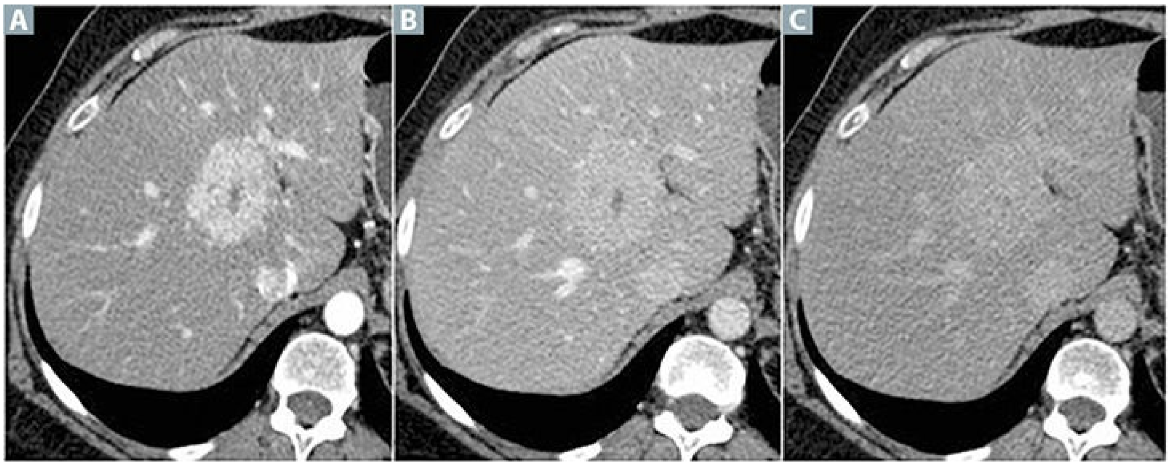


FIGURE 2.6-39. **Contrast-enhanced arterial phase CT scan of focal nodular hyperplasia (FNH). (A)** an axial view of the liver with FNH is seen during the arterial phase of contrast administration. **(B)**, the portal phase is seen of this same liver lesions demonstrating washout (loss of brightness) of this lesion. **(C)** delayed imaging (taken after the portal venous phase) revealing further washout of the liver lesion. All three images reveal a hypodense, central, stellate-shaped region in this lesion.(Adapted with permission from Scialpi M, Pierotti L, Gravante S, et al. Split-bolus versus triphasic multidetector-row computed tomography technique in the diagnosis of hepatic focal nodular hyperplasia: A case report. *J Med Case Rep.* 2014;8:425.)

- ***Tx:*** In asymptomatic individuals, no intervention necessary. For those who are symptomatic, recommendations for intervention may be made (eg, surgical resection, transarterial embolization, radiofrequency ablation).

A

The most likely diagnosis is nonalcoholic fatty liver disease (NAFLD), a condition that is associated with insulin resistance and metabolic syndrome.

Hepatic Hemangioma

Aberrant collection of blood vessels within the liver. Pathogenesis not well understood, but thought to be due to congenital vascular lesions that develop into hemangiomas through the process of ectasia over time. Generally asymptomatic. Most common benign liver lesion

- ***Hx/PE:*** Typically asymptomatic and discovered incidentally on contrast-enhanced imaging.
- ***Dx:*** Contrast-enhanced imaging revealing arterial phase enhancement with heterogenous washout on portal phase imaging.
- ***Tx:*** No intervention required for lesions <5 mm that are asymptomatic. Lesions >5 mm should have follow-up; MRI should be performed in 6 to 12 months. If the lesion grows in size >3 mm per year on surveillance imaging, repeat surveillance imaging should be obtained in 6 to 12 months. If it continues to show a growth rate >3 mm/year, multidisciplinary evaluation for possible intervention should be obtained. If the lesion is stable (growth rate <3 mm/year), no further surveillance imaging is required.

Hepatic Adenoma (Hepatocellular Adenoma)

Rare benign liver tumor with risk of rupture and subsequent intraperitoneal hemorrhage. Associated especially with use of oral contraceptives, but also associated with obesity, FAP, and glycogen storage diseases.

- ***Hx/PE:*** Tends to present asymptomatically in patients taking oral contraceptive medications, but can also present with life-threatening intraperitoneal hemorrhage from adenoma rupture manifesting as sudden-onset severe abdominal pain with signs of hypotension.
- ***Dx:*** May be discovered incidentally on imaging or in a patient with signs of hemorrhagic shock from adenoma rupture and subsequent intraperitoneal bleeding.
- ***Tx:*** For asymptomatic individuals with lesions <5 cm, discontinuation of oral contraceptives and weight loss/lifestyle modifications to achieve ideal body weight in addition to 6-month surveillance imaging with contrast-enhanced MRI. If there is no increase in size on 6-month follow up, annual MRI surveillance imaging is recommended. If there is increase in size, surgical resection is recommend. For lesions >5 cm or symptomatic, surgical resection is recommended due to increased risk of hemorrhage.

Hepatic Abscess

Liver abscesses are the most common visceral abscess. Most liver abscesses are polymicrobial, with most pathogens being mixed enteric facultative and anaerobic species.

- ***Risk factors:*** DM, underlying hepatobiliary/pancreatic disease, liver transplant, and regular use of PPIs.
- ***Hx/PE:*** Fever, abdominal pain, nausea/vomiting, anorexia, weight loss, and malaise.
- ***Dx:*** Multiple space-occupying lesions on abdominal imaging. A CT of the abdomen and pelvis will typically reveal a well-defined lesion with peripheral rim-enhancement and central hypoattenuation (see Fig. 2.6-40); however, they can be loculated with subcollections and have an irregular border. Laboratory evaluation will likely reveal transaminitis and hyperbilirubinemia. Definitive diagnosis can be made with image-

guided aspiration and drainage revealing purulent material or bacteria identified on Gram stain/culture of the aspirate material.

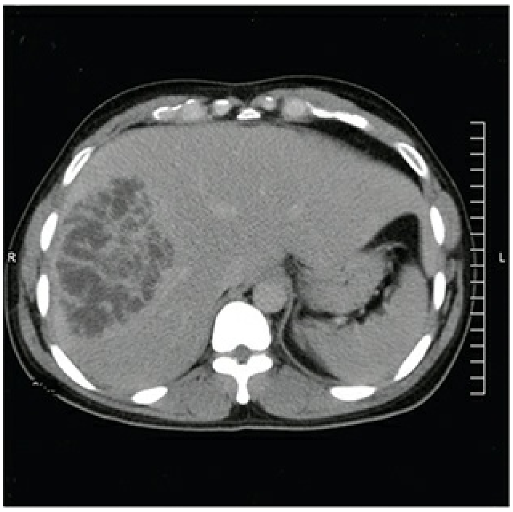


FIGURE 2.6-40. **CT of the abdomen with contrast enhancement revealing a multiloculated, rim-enhancing hepatic abscess.** (Adapted with permission from Casella F, Finazzi L, Repetti V, et al. Liver abscess caused by Klebsiella pneumoniae: Two case reports. *Cases J.* 2009;2:6879.)

- ***Tx:*** Image-guided aspiration or drainage and empiric antibiotic therapy.

Hydatid Cyst

Triggered by infection with *Echinococcus granulosus*, which causes cystic echinococcus infection (also called hydatid disease or hydatidosis).

- ***Risk factors:*** Exposure through ingestion of parasite egg in contaminated food, water, soil or by direct contact with animal hosts (dogs are definitive hosts).
- ***Hx/PE:*** May cause asymptomatic incubation that lasts several years. Hydatid cysts only manifest with symptoms when they get large enough. Patients typically present with abdominal pain and nausea/vomiting.
- ***Dx:*** Imaging of the abdomen, typically by ultrasound revealing an anechoic, smooth, round cyst, typically with "daughter" cysts, which may have echogenic material between the cysts. Imaging findings in combination with laboratory evaluation via enzyme-linked immunosorbent assay (ELISA) serologic testing makes the diagnosis. In the absence of positive serologic tests, percutaneous aspiration or biopsy may be required to confirm the diagnosis.
- ***Tx:*** Antiparasitic therapy in combination with either surgical resection or cyst aspiration.

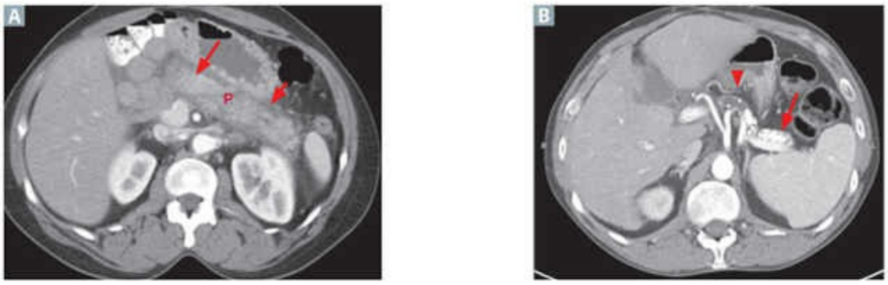
PANCREATIC DISEASE

PANCREATITIS

Table 2.6-24 outlines the features of acute and chronic pancreatitis.

TABLE 2.6-24. **Features of Acute and Chronic Pancreatitis**

VARIABLE	ACUTE PANCREATITIS	CHRONIC PANCREATITIS
Pathophysiology	Leakage of activated pancreatic enzymes into pancreatic and peripancreatic tissue	Irreversible parenchymal destruction leading to pancreatic dysfunction and insufficiency
Time course	Abrupt onset of severe pain	Persistent, recurrent episodes of severe pain
Etiology/risk factors	Gallstones, alcohol abuse, hypercalcemia, hypertriglyceridemia, trauma (most common cause of acute pancreatitis in children), drug side effects (thiazide diuretics), viral infections, post-ERCP, scorpion sting	Alcohol abuse (90%), gallstones, cystic fibrosis CF, smoking, pancreatic divisum, family history autoimmune (IgG4) pancreatitis
History/PE	Severe epigastric pain (radiating to the back); nausea, vomiting, weakness, fever, shock, pleural effusions, acute respiratory distress syndrome (ARDS) Flank bruising (Grey Turner sign) and periumbilical discoloration (Cullen sign) may be evident on exam	Recurrent episodes of persistent epigastric pain; anorexia, nausea, constipation, flatulence, steatorrhea, weight loss, DM
Diagnosis	↑ lipase (more sensitive and specific than amylase), ↑ amylase, ↓ calcium if severe; "sentinel loop" or "colon cutoff sign" on x-ray of the abdomen Ultrasound of the abdomen or CT may show an enlarged pancreas with peripancreatic fluid and fat stranding (arrows in Image A), abscess, hemorrhage, necrosis, or pseudocyst	↑ to normal amylase and lipase, ↓ stool elastase, pancreatic calcifications (arrows in Image B), and alternating stenosis and dilation (arrowhead in Image B) of the main pancreatic duct on CT or ultrasound ("chain of lakes")
Treatment	Removal of the offending agent if possible Supportive care, including IV fluids/electrolyte replacement, analgesia, bowel rest, NG suction, nutritional support, and O_2 Infected pancreatic necrosis should be treated with antibiotics, though prophylactic antibiotics are not recommended Endoscopic, percutaneous, or surgical debridement may be considered	Analgesia, pancreatic enzyme replacement, avoidance of causative agents (EtOH), celiac nerve block; endoscopic dilation of pancreatic duct; surgery for intractable pain or structural causes
Prognosis	Roughly 85%–90% are mild and self-limited; 10%–15% are severe, requiring ICU admission Mortality may approach 50% in severe cases	Patients can have chronic pain and pancreatic dysfunction
Complications	Pancreatic pseudocyst, fistula formation, hypocalcemia, renal failure, pleural effusion, chronic pancreatitis, sepsis, and ARDS Mortality secondary to acute pancreatitis can be predicted with Ranson criteria	Chronic pain, opiate addiction, diabetes mellitus, malnutrition/weight loss, splenic vein thrombosis, pancreatic cancer



P, Pancreas. (Images reproduced with permission from USMLE-Rx.com.)

PANCREATIC CYSTS

Pancreatic cysts are common incidental findings on imaging in older populations (>70 years of age).

- ***Hx/PE:*** Usually detected incidentally on imaging being performed for an unrelated reason.
- ***Dx:*** Most manageable with imaging surveillance. Some may require further workup, based on presence/absence of "red flag features" on radiographic evaluation.
  - Red flag features include large size (>3 cm), solid components or calcifications, main pancreatic duct involvement (as evidenced by ductal dilation on imaging), or

thickened/irregular cystic walls.

- The presence of these red flag signs increases risk of malignant transformation of the pancreatic cystic lesion and requires further workup via EUS-guided biopsy.
- Occasionally, a surgeon may opt to immediately resect the lesion without prior biopsy if the lesion identified is determined to be very high risk.

KEY FACT

Red flag features of pancreatic cystic lesions on radiography:

- Large size (>3 cm)
- Solid components or calcifications
- Main pancreatic duct involvement (as evidenced by ductal dilation on imaging)
- Thickened or irregular cystic wall

PANCREATIC NEUROENDOCRINE TUMORS (PNETs)

Insulinoma

Results from insulin-producing tumor, associated with multiple endocrine neoplasia (MEN) type 1, usually benign.

History

Hypoglycemia satisfying Whipple triad: (1) documented hypoglycemia on a venipuncture; (2) associated symptoms, including sweating, palpitations, anxiety, tremors, headache, and confusion; and (3) resolution of symptoms with correction of hypoglycemia

Diagnosis

- **Best initial test:** Fasting serum insulin (elevated), C-peptide (elevated).
- **Most accurate test:** 72-hour fasting. Patient develops profound or symptomatic hypoglycemia after prolonged fast. Once hypoglycemia is reached, labs drawn to determine etiology include glucose, serum insulin level (elevated), C-peptide level (elevated), sulfonylurea screen (⊖), serum β-hydroxybutyrate level (low), and serum cortisol level (normal/elevated).

Treatment

Surgery to resect tumor.

VIPoma

Results from VIP-producing tumor; highly malignant.

History

Watery diarrhea, dehydration, muscle weakness, flushing.

Diagnosis

- **Stool sample:** Low stool osmotic gap (ie, secretory diarrhea)
- **Lab tests:** High VIP levels, achlorhydria (since VIP inhibits gastrin secretion), hyperglycemia, hypercalcemia, hypokalemia
- **CT scan:** Localization of tumor

Treatment

Initially, replacement of fluid and electrolyte losses. Surgery to resect tumor. May also consider octreotide.

Somatostatinoma

Results from somatostatin-producing tumor originating from D cells. May occur as part of MEN type 1 syndrome. Usually found in the pancreatic head but may also be found in the duodenum.

- ***Hx/PE:*** Generally speaking, symptoms nonspecific. Presents with abdominal pain and weight loss. Rarely, presents with somatostatinoma syndrome, which should be suspected in those who have the triad of cholelithiasis, diarrhea/steatorrhea, and diabetes/glucose intolerance.
- ***Dx:*** Usually found on imaging incidentally through the evaluation of abdominal pain. The best test to establishing diagnosis: EUS with FNA.
- ***Tx:*** In those with nonmetastatic disease, surgical resection is the treatment of choice. Surgical resection is usually manageable with a pancreaticoduodenectomy (Whipple procedure). Treatment in those with metastatic disease is dependent on the extent and location of metastasis. Symptomatic treatment with somatostatin analogs (eg, octreotide) to inhibit somatostatin secretion is also used.

Gastrinoma

Results from gastrin-producing tumor originating from G cells. See “Zollinger-Ellison Syndrome” for more information.

PANCREATIC CANCER

Most (75%) are adenocarcinomas in the head of the pancreas. Risk factors include smoking, chronic pancreatitis, and a first-degree relative with pancreatic cancer. Incidence ↑ after 45 years of age; pancreatic cancer is slightly more common in males.

History/PE

- Abdominal pain radiating toward the back, obstructive jaundice, loss of appetite, nausea, vomiting, weight loss, weakness, fatigue, and indigestion. Often asymptomatic and thus presents late in the disease course. In some patients, depression most prominent symptom.
- May reveal a palpable, nontender gallbladder (Courvoisier sign) or migratory thrombophlebitis (Trousseau syndrome).

KEY FACT

The hallmark finding in pancreatic cancer is a nontender, palpable gallbladder and jaundice.

Diagnosis

Best initial test: CT scan with contrast. Localization of the tumor and assessment of the extent of local invasion and distant metastases. Ultrasound of the abdomen initial test of choice if the patient suspected of having pancreatic cancer also has jaundice. If mass not visualized on CT/ultrasound, ERCP indicated. CA-19-9 often elevated, but is neither sensitive nor specific.

Treatment

- **Locally advanced or metastatic disease:** Most frequent presentation. Palliative chemotherapy or best supportive care.
- **Small tumors in the pancreatic head with no metastasis or major vessel involvement:** Whipple procedure (pancreaticoduodenectomy).
- **Tumors in the body or tail of the pancreas with no metastasis or celiac artery involvement:** Distal pancreatotomy and splenectomy. Chemotherapy with fluorouracil (5-FU) and gemcitabine to possibly improve short-term survival, but long-term prognosis poor (5%–10% 5-year survival). ERCP with stenting to relieve patients presenting with obstructive symptoms.

NOTES

HIGH-YIELD FACTS IN

HEMATOLOGY

- Coagulation Disorders
  - NORMAL HEMOSTASIS
  - TRANSFUSION PRODUCTS
  - HEMOPHILIA
  - VON WILLEBRAND DISEASE
- Hypercoagulable States
  - ACTIVATED PROTEIN C (APC) RESISTANCE/FACTOR V LEIDEN
  - HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)
  - ANTIPHOSPHOLIPID SYNDROME
  - DISSEMINATED INTRAVASCULAR COAGULATION
- Platelet Disorders
  - THROMBOTIC THROMBOCYTIC PURPURA
  - HEMOLYTIC UREMIC SYNDROME
  - IDIOPATHIC THROMBOCYTOPENIC PURPURA (IMMUNE THROMBOCYTOPENIA)
- Red Blood Cell Disorders
  - ANEMIAS
  - MICROCYTIC ANEMIAS
  - NONHEMOLYTIC, NORMOCYTIC ANEMIAS
  - HEMOLYTIC, NORMOCYTIC ANEMIAS
  - G6PD DEFICIENCY
  - PAROXYSMAL NOCTURNAL HEMOGLOBINURIA
  - HEREDITARY SPHEROCYTOSIS
  - AUTOIMMUNE HEMOLYTIC ANEMIA
  - MEGALOBLASTIC, MACROCYTIC ANEMIA
  - PORPHYRIAS
  - POLYCYTHEMIAS
  - BLOOD TRANSFUSION REACTIONS
- White Blood Cell Disorders
  - NEUTROPENIA
  - LYMPHOPENIA AND EOSINOPENIA
  - EOSINOPHILIA
  - LEUKEMIAS
  - CHRONIC MYELOGENOUS LEUKEMIA
  - LYMPHOMAS
- Plasma Cell Disorders
  - MULTIPLE MYELOMA
  - WALDENSTRÖM MACROGLOBULINEMIA
  - AMYLOIDOSIS
- Transplant Medicine

Multisystem Hematology
  HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS
  MASTOCYTOSIS
  LANGERHANS CELL HISTIOCYTOSIS

COAGULATION DISORDERS

NORMAL HEMOSTASIS

Normal hemostasis is a regulated, dynamic process between thrombin-stimulated fibrin clot formation and plasmin-induced clot lysis. It is divided into three phases: vascular phase (spasm), platelet phase (plug), and coagulation phase.

- The **vascular phase** is a brief contraction of blood vessels at the site of vessel injury.
- The **platelet phase** is first activated at the site of vascular injury to form a platelet plug. It can be further subdivided into:
  - The adhesion of platelets to the disrupted endothelium, which is mediated by the binding of the platelet surface receptor GPIb to von Willebrand factor (vWF)
  - The aggregation of platelets at the site of bleeding mediated by the binding of the GPIIb/IIIa receptor on the platelet surface
  - Platelet function monitored by bleeding time
- The **coagulation phase** can be further subdivided based on commonly obtained laboratory tests into:
  - The extrinsic pathway (fewer factors [factor VII and tissue factor] monitored by prothrombin time [PT]).
  - The intrinsic pathway (more factors [factors VIII, IX, XI, and XII] monitored by partial thromboplastin time [PTT]).
  - Both of these pathways converge into the common pathway (factors I, II, X, XIII). See Figure 2.7-1.

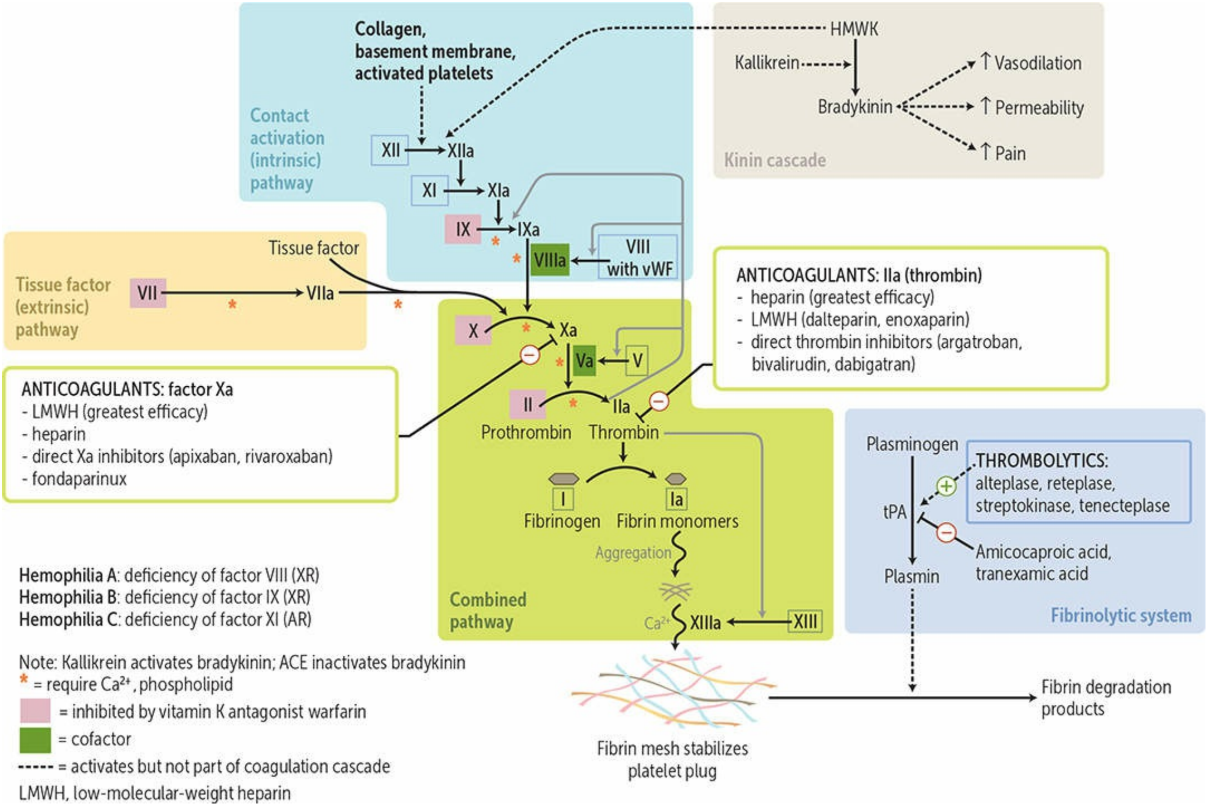

Collagen, basement membrane, activated platelets
Contact activation (intrinsic) pathway
XII
XIIa
XI
XIa
IX
IXa
VIIIa
VIII with vWF
HMWK
Kallikrein
Bradykinin
↑ Vasodilation
↑ Permeability
↑ Pain
Kinin cascade
Tissue factor
Tissue factor (extrinsic) pathway
VII
VIIa
ANTICOAGULANTS: IIa (thrombin)
- heparin (greatest efficacy)
- LMWH (dalteparin, enoxaparin)
- direct thrombin inhibitors (argatroban, bivalirudin, dabigatran)
X
Xa
Va
V
II
IIa
Prothrombin
Thrombin
ANTICOAGULANTS: factor Xa
- LMWH (greatest efficacy)
- heparin
- direct Xa inhibitors (apixaban, rivaroxaban)
- fondaparinux
I
Ia
Fibrinogen
Fibrin monomers
Aggregation
Plasminogen
tPA
Plasmin
THROMBOLYTICS: alteplase, reteplase, streptokinase, tenecteplase
Amicocaproic acid, tranexamic acid
Fibrinolytic system
Hemophilia A: deficiency of factor VIII (XR)
Hemophilia B: deficiency of factor IX (XR)
Hemophilia C: deficiency of factor XI (AR)
Combined pathway
Ca²⁺
XIIIa
XIII
Note: Kallikrein activates bradykinin; ACE inactivates bradykinin
* = require Ca²⁺, phospholipid
= inhibited by vitamin K antagonist warfarin
= cofactor
----- = activates but not part of coagulation cascade
LMWH, low-molecular-weight heparin
Fibrin mesh stabilizes platelet plug
Fibrin degradation products

FIGURE 2.7-1. Coagulation cascade. *HMWK*, High-molecular-weight kininogen; *LMWH*, low-molecular-weight heparin; *vWF*, von Willebrand factor. (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

Tissue plasminogen activators are contraindicated in:

- Active bleeding or risk of bleeding
- A known intracranial lesion
- Recent (<2 months) trauma or surgery to the spine or brain
- History of a hemorrhagic stroke or evidence of a nonhemorrhagic stroke in the past 3 months

In the setting of bleeding dysfunction, bleeding time PT and/or PTT may be prolonged, depending on the causes of bleeding.

Vascular injury leads to the release of vWF and tissue factor from subendothelial vessel walls.

- vWF facilitates adhesion and aggregation of platelets, forming a platelet plug.
- Tissue factor triggers the coagulation cascade via the extrinsic pathway with factor VII.

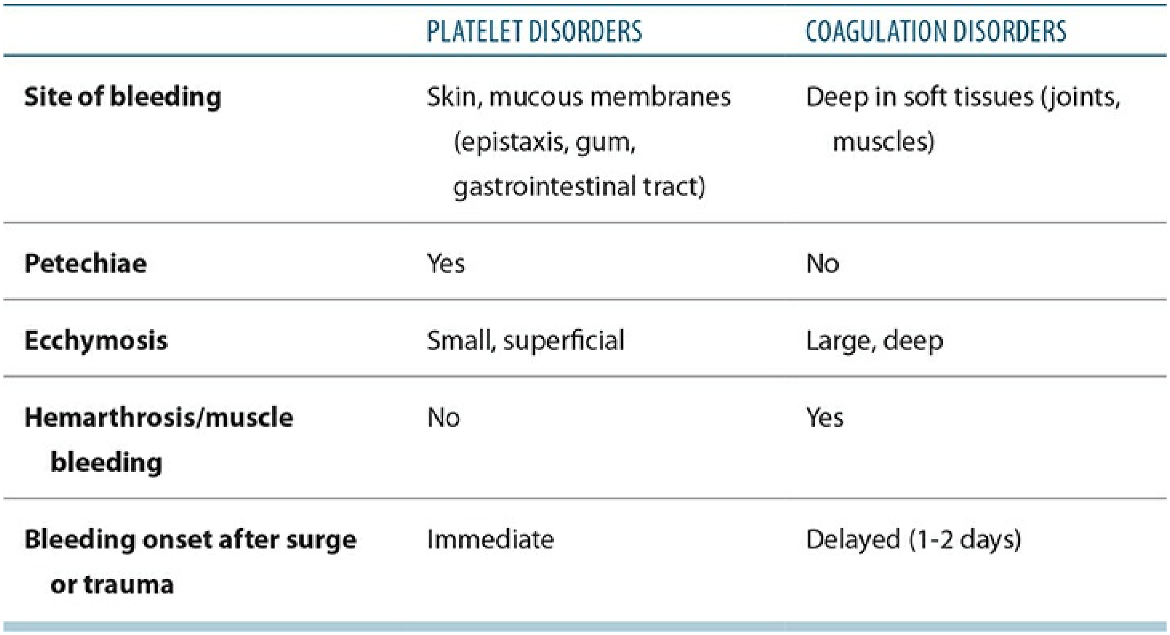
KEY FACT

Enteric bacteria synthesize vitamin K. Neonates lack these bacteria and are prone to bleeding, which is why vitamin K is given at birth.
Similarly, in children and adults, prolonged use of antibiotics could affect the normal flora,

and therefore antibiotics could increase the bleeding tendency.

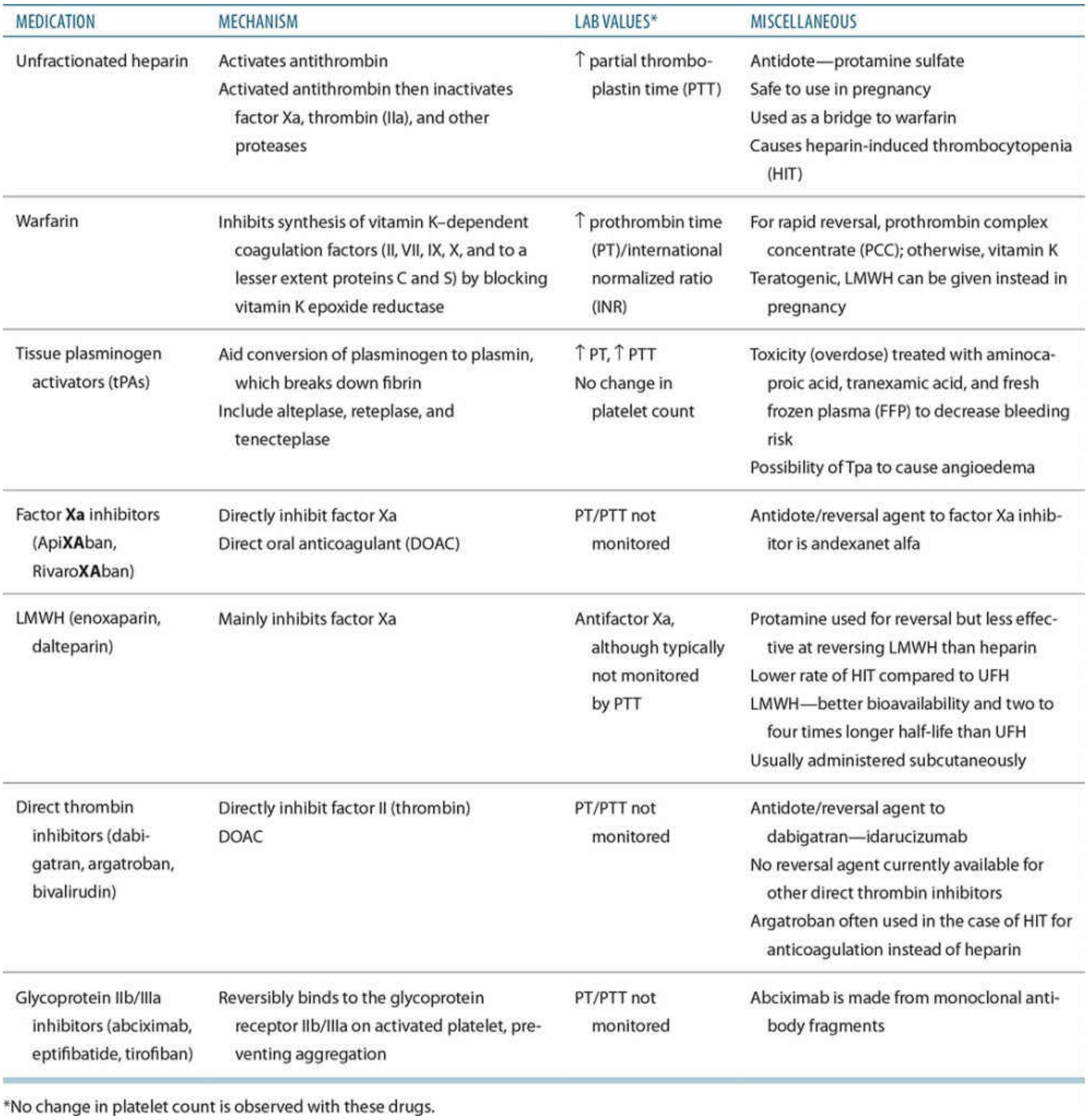
Ultimately the platelet plug and coagulation cascade create a fibrin mesh, as shown in Figure 2.7-1. Common findings seen in platelet vs coagulation disorders can be found in Table 2.7-1. Drugs affecting the cascade are shown in Table 2.7-2.

TABLE 2.7-1. Features of Bleeding Disorders



	PLATELET DISORDERS	COAGULATION DISORDERS
Site of bleeding	Skin, mucous membranes (epistaxis, gum, gastrointestinal tract)	Deep in soft tissues (joints, muscles)
Petechiae	Yes	No
Ecchymosis	Small, superficial	Large, deep
Hemarthrosis/muscle bleeding	No	Yes
Bleeding onset after surge or trauma	Immediate	Delayed (1-2 days)

TABLE 2.7-2. Coagulation Pharmacology



MEDICATION	MECHANISM	LAB VALUES*	MISCELLANEOUS
Unfractionated heparin	Activates antithrombin Activated antithrombin then inactivates factor Xa, thrombin (IIa), and other proteases	↑ partial thromboplastin time (PTT)	Antidote—protamine sulfate Safe to use in pregnancy Used as a bridge to warfarin Causes heparin-induced thrombocytopenia (HIT)
Warfarin	Inhibits synthesis of vitamin K–dependent coagulation factors (II, VII, IX, X, and to a lesser extent proteins C and S) by blocking vitamin K epoxide reductase	↑ prothrombin time (PT)/international normalized ratio (INR)	For rapid reversal, prothrombin complex concentrate (PCC); otherwise, vitamin K Teratogenic, LMWH can be given instead in pregnancy
Tissue plasminogen activators (tPAs)	Aid conversion of plasminogen to plasmin, which breaks down fibrin Include alteplase, reteplase, and tenecteplase	↑ PT, ↑ PTT No change in platelet count	Toxicity (overdose) treated with aminocaproic acid, tranexamic acid, and fresh frozen plasma (FFP) to decrease bleeding risk Possibility of Tpa to cause angioedema
Factor **Xa** inhibitors (Api**XA**ban, Rivaro**XA**ban)	Directly inhibit factor Xa Direct oral anticoagulant (DOAC)	PT/PTT not monitored	Antidote/reversal agent to factor Xa inhibitor is andexanet alfa
LMWH (enoxaparin, dalteparin)	Mainly inhibits factor Xa	Antifactor Xa, although typically not monitored by PTT	Protamine used for reversal but less effective at reversing LMWH than heparin Lower rate of HIT compared to UFH LMWH—better bioavailability and two to four times longer half-life than UFH Usually administered subcutaneously
Direct thrombin inhibitors (dabigatran, argatroban, bivalirudin)	Directly inhibit factor II (thrombin) DOAC	PT/PTT not monitored	Antidote/reversal agent to dabigatran—idarucizumab No reversal agent currently available for other direct thrombin inhibitors Argatroban often used in the case of HIT for anticoagulation instead of heparin
Glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban)	Reversibly binds to the glycoprotein receptor IIb/IIIa on activated platelet, preventing aggregation	PT/PTT not monitored	Abciximab is made from monoclonal antibody fragments

*No change in platelet count is observed with these drugs.

A heparin-to-warfarin bridge is necessary because the onset of anticoagulation with warfarin is slow. Concurrent initiation with heparin is needed until warfarin dosing is adjusted to reach an international normalized ratio (INR) in the therapeutic range (2-3). In addition, proteins C and S have shorter half-lives than the other vitamin K–dependent factors (II, VII, IX, and X), leading to a transient period of paradoxical hypercoagulability before proper anticoagulation.

Warfarin vs DOAC pharmacology can be found in Table 2.7-3 and treatment of a supratherapeutic INR secondary to warfarin use can be found in Table 2.7-4.

TABLE 2.7-3. Warfarin vs DOACs Pharmacology

	WARFARIN	DOAC
Mechanism of action	Inhibits vitamin K epoxide reductase	Inhibits Factor Xa or thrombin
Laboratory monitoring	PT/INR	Not needed
Antidote	Vitamin K, FFP, PCC	Idarucizumab for dabigatran Andexanet alfa for factor Xa inhibitor
Half-life	Long	Short
Onset	Slow	Rapid
Offset	Prolonged	Short
Metabolism	Hepatic	Renal
Special populations	Patients with mechanical valves (warfarin preferred), poor medication adherence (avoid warfarin), CKD (avoid warfarin)	Pregnant patients Patients with cirrhosis
Cost	Low	High

DOAC, Direct oral anticoagulant.

TABLE 2.7-4. **Treatment of Supratherapeutic INR Due to Warfarin**

	MANAGEMENT
Bleeding	Discontinue warfarin, administer vitamin K IV and PCC. Monitor INR closely.
INR >10 without bleeding	Discontinue warfarin, administer oral vitamin K. Monitor INR closely.
INR 4.5-10 without bleeding	Hold warfarin temporarily for few doses; can administer low-dose oral vitamin K.
INR <4.5 without bleeding	Hold the next dose of warfarin and readjust the maintenance dose of warfarin.

KEY FACT

The liver is the machinery responsible for synthesizing the vitamin K–dependent coagulation factors. Liver disease can therefore increase the bleeding tendency.

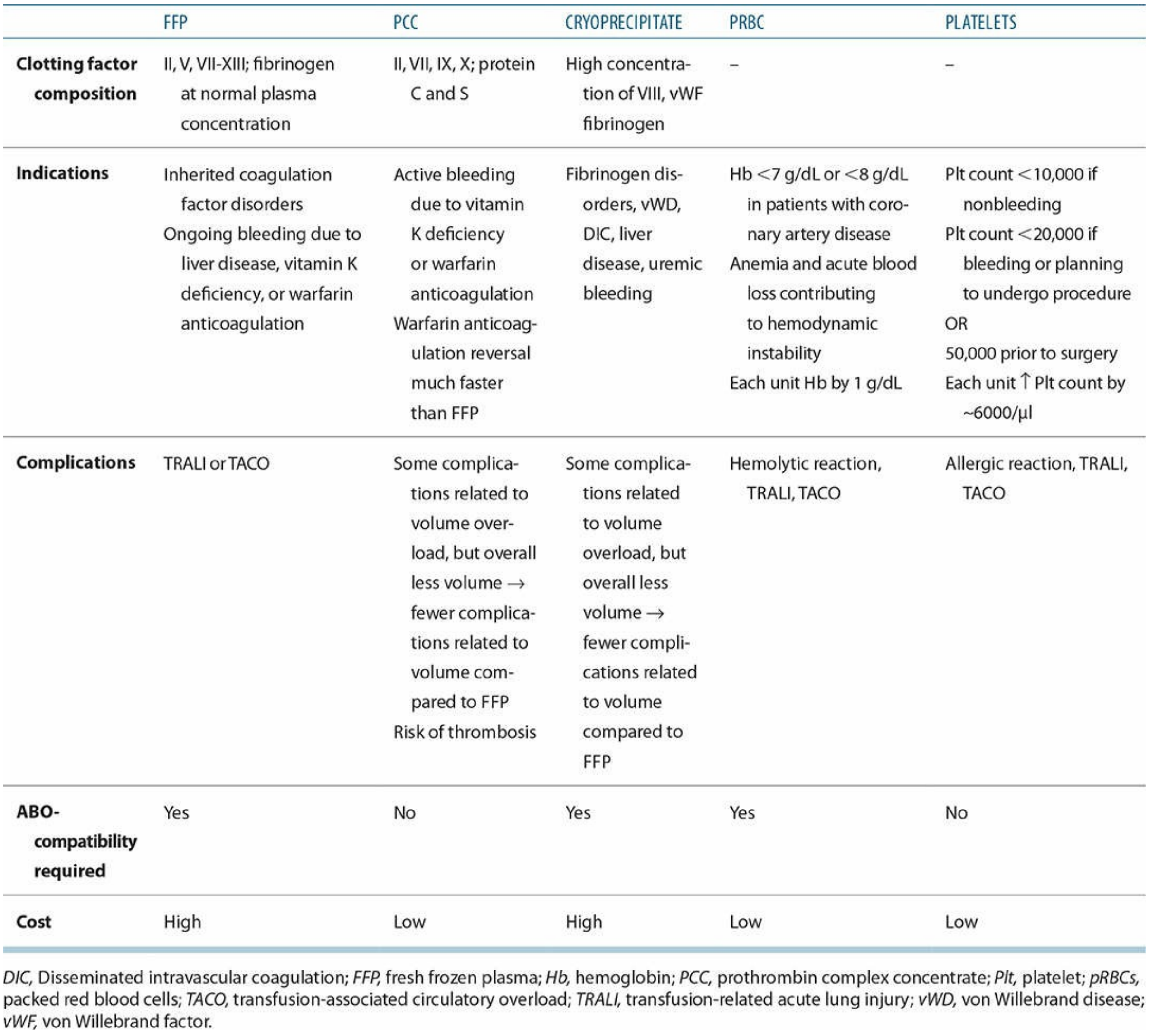
Q

An 8-year-old boy from Eastern Europe presents with severe swelling and warmth of his knee several hours after a minor “bump” against a lamppost. What is the most accurate diagnostic test for his presentation?

TRANSFUSION PRODUCTS

Many different blood products are transfused for a variety of reasons. Common blood replacement product composition, indications, and complications are discussed in Table 2.7-5.

TABLE 2.7-5. Features of Blood Replacement Products



	FFP	PCC	CRYOPRECIPITATE	PRBC	PLATELETS
Clotting factor composition	II, V, VII-XIII; fibrinogen at normal plasma concentration	II, VII, IX, X; protein C and S	High concentration of VIII, vWF fibrinogen	–	–
Indications	Inherited coagulation factor disorders Ongoing bleeding due to liver disease, vitamin K deficiency, or warfarin anticoagulation	Active bleeding due to vitamin K deficiency or warfarin anticoagulation Warfarin anticoagulation reversal much faster than FFP	Fibrinogen disorders, vWD, DIC, liver disease, uremic bleeding	Hb <7 g/dL or <8 g/dL in patients with coronary artery disease Anemia and acute blood loss contributing to hemodynamic instability Each unit Hb by 1 g/dL	Plt count <10,000 if nonbleeding Plt count <20,000 if bleeding or planning to undergo procedure OR 50,000 prior to surgery Each unit ↑ Plt count by ~6000/μl
Complications	TRALI or TACO	Some complications related to volume overload, but overall less volume → fewer complications related to volume compared to FFP Risk of thrombosis	Some complications related to volume overload, but overall less volume → fewer complications related to volume compared to FFP	Hemolytic reaction, TRALI, TACO	Allergic reaction, TRALI, TACO
ABO-compatibility required	Yes	No	Yes	Yes	No
Cost	High	Low	High	Low	Low

DIC, Disseminated intravascular coagulation; *FFP,* fresh frozen plasma; *Hb,* hemoglobin; *PCC,* prothrombin complex concentrate; *Plt,* platelet; *pRBCs,* packed red blood cells; *TACO,* transfusion-associated circulatory overload; *TRALI,* transfusion-related acute lung injury; *vWD,* von Willebrand disease; *vWF,* von Willebrand factor.

A

This boy probably has (X-linked) hemophilia A (most common), which is most accurately diagnosed with a specific factor VIII level.

HEMOPHILIA

Clotting factor deficiencies of factors VIII (hemophilia A, 80% of cases); IX (hemophilia B); and XI (hemophilia C), which ↑ tendency to bleed. Hemophilia A and B are X-linked recessive genetic disorders (1:10,000 male births). Rarely, hemophilias can be acquired if antibodies against these factors are produced as a result of autoimmune diseases, lymphoproliferative disorders, or postpartum states.

KEY FACT

Hemophilia A and hemophilia B are X-linked recessive genetic disorders. Hemophilia C is most common in people with Ashkenazi Jewish heritage, and it is often autosomal recessive.

History/PE

- Hemophilia presents in a young male (think child that is beginning to walk; 1–2 years of age) with spontaneous bleeding into the tissues, muscles, and joints (hemarthrosis) that, if untreated, can lead to irreversible debilitating arthropathy and joint destruction caused by hemosiderin deposition, destruction of the cartilage and synovium (the lining of the joint), and fibrosis. Joint x-ray will show calcifications.
- Spontaneous intracerebral, renal, retroperitoneal, and gastrointestinal (GI) hemorrhages are also seen.
- Mild cases may have major hemorrhage after surgery, trauma, or dental procedures, but they are otherwise asymptomatic.

Diagnosis

- Prolonged PTT (VIII, IX, and XI are all the factors of intrinsic pathway) on basic bleeding workup. PT and bleeding time are normal.
- **Best initial test:** Mixing study. Mixing the patient’s plasma with normal plasma will correct the PTT in hemophilia patients because normal plasma contains all clotting factors and will replace the missing clotting factor (Fig. 2.7-2).

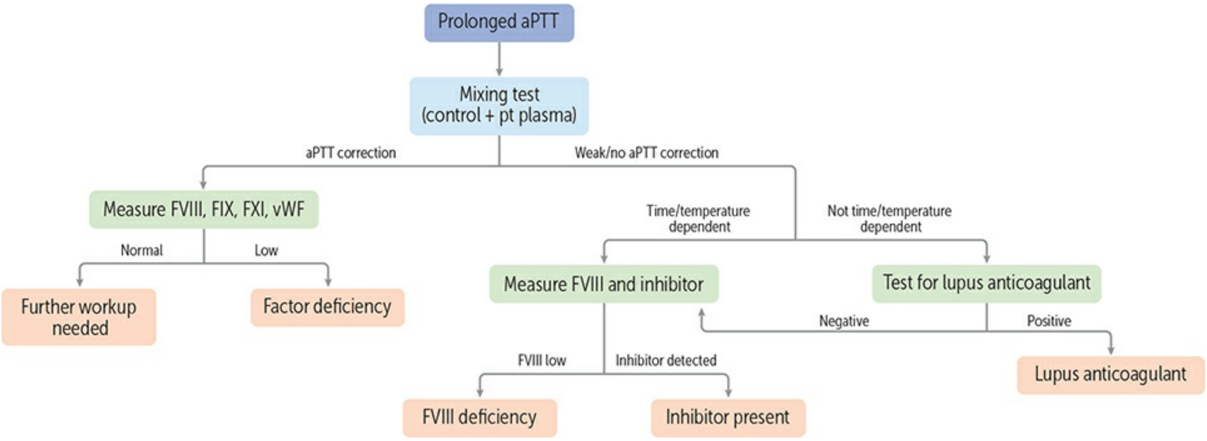

Prolonged aPTT
Mixing test (control + pt plasma)
aPTT correction
Weak/no aPTT correction
Measure FVIII, FIX, FXI, vWF
Normal
Low
Further workup needed
Factor deficiency
Time/temperature dependent
Not time/temperature dependent
Measure FVIII and inhibitor
Test for lupus anticoagulant
Negative
Positive
Lupus anticoagulant
FVIII low
Inhibitor detected
FVIII deficiency
Inhibitor present

FIGURE 2.7-2. **Workup of prolonged PPT in patients with suspected factor deficiency.** *aPTT*, Activated partial thromboplastin time. (Reproduced with permission from USMLE-Rx.com.)

- In cases of acquired hemophilia, adding the missing factor will not correct the PTT due to the presence of antibodies directed at the missing factor.
- **Most accurate test:** Specific factor assays for factors VII, VIII, IX, XI, and XII

KEY FACT

Cryoprecipitate consists mainly of factor VIII and fibrinogen, with smaller concentrations of factor XIII, Vwf, and fibronectin. It is a more concentrated source of factor VIII and fibrinogen than FFP.

Treatment

- Cases in which bleeding is severe or the factor level is ≤1% of normal (severe) call for immediate transfusion with the missing factor; if that is unavailable, cryoprecipitate can be used.
- If bleeding is not severe and factor level is >5% of normal (mild) or 1% to 5% of normal (moderate), hemophilia A may be treated with desmopressin, which releases factor VIII from the endothelial cells.
- Genetic counseling may be required to screen other family members.
- Prophylactic administration of clotting factor concentrates is the basis of modern treatment of severe hemophilia A.

VON WILLEBRAND DISEASE

Von Willebrand disease (vWD) is the most common inherited bleeding disorder (1% of the population). It results from an autosomal dominant defect or a deficiency in vWF with a potential decrease in the levels of factor VIII, which is carried by vWF (see Fig. 2.7-3). The three main roles of vWF are to (1) bring platelets to the exposed subendothelium, (2) aggregate platelets, and (3) bind to factor VIII. Symptoms of vWD are caused by platelet dysfunction and deficient factor VIII but are milder than in hemophilia.

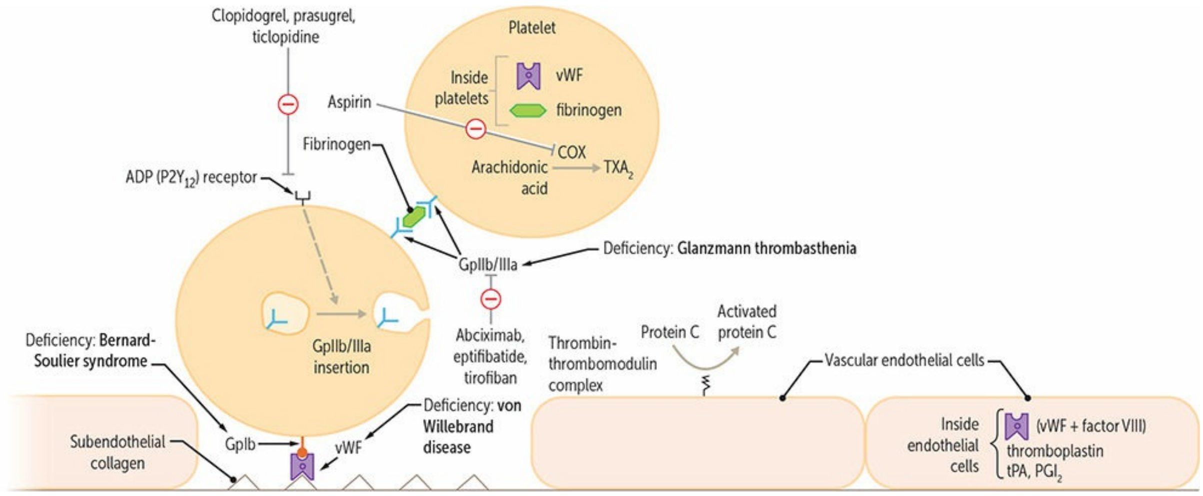

Clopidogrel, prasugrel, ticlopidine
Aspirin
Platelet
Inside platelets
vWF
fibrinogen
Fibrinogen
COX
Arachidonic acid
TXA_2
ADP ($P2Y_{12}$) receptor
GpIIb/IIIa
Deficiency: **Glanzmann thrombasthenia**
GpIIb/IIIa insertion
Abciximab, eptifibatide, tirofiban
Deficiency: **Bernard-Soulier syndrome**
Thrombin-thrombomodulin complex
Protein C
Activated protein C
Vascular endothelial cells
Deficiency: **von Willebrand disease**
Subendothelial collagen
GpIb
vWF
Inside endothelial cells
(vWF + factor VIII)
thromboplastin
tPA, PGI_2

FIGURE 2.7-3. **Thrombogenesis deficiencies.** *ADP*, Adenosine diphosphate; *COX*, cyclooxygenase; *PGI_2*, prostacyclin; *tPA*, tissue plasminogen activator; *TXA_2*, thromboxane

A2; *vWF*, von Willebrand factor. (Adapted with permission from USMLE-Rx.com.)

The most common form of vWD is type 1 vWD (Mild to moderate quantitative deficiency in vWF). Type 2 vWD includes qualitative defects in vWF, and type 3 vWD is complete quantitative loss of vWF.

Heyde syndrome is a multisystem disorder characterized by the triad of aortic stenosis (AS), GI bleeding, and acquired von Willebrand syndrome, which results from the increased circulatory shear forces and subsequent cleavage and loss of vWF.

KEY FACT

vWD often presents with a positive family history of bleeding tendency, normal platelet count, and clinical manifestations of platelet dysfunction such as epistaxis, menorrhagia, and others.

History/PE

- Often presents in childhood with recurrent and prolonged mucosal bleeding (epistaxis, gums, gingival, menorrhagia) and bleeding after dental or surgical procedures
- Family history often present
- Worsening of symptoms with acetylsalicylic acid (ASA) use

KEY FACT

Reduced agglutination is seen on the ristocetin cofactor assay (detects vWF dysfunction); it is diagnostic of vWD and helps to distinguish it from other platelet disorders, such as Bernard-Soulier syndrome.

Diagnosis

- **Best initial diagnostic test:** Ristocetin cofactor assay of patient plasma diagnostic. It measures the capacity of vWF to agglutinate platelets and detects vWF dysfunction.
- **Additional diagnostic test:** vWF antigen level. ↓ levels of antigen may be present. Factor VIII levels can also be used to detect vWF dysfunction, but this is less specific.
- Initial bleeding workup showing an ↑ bleeding time in all vWD types. ↑ PTT as in hemophilia may be seen, which is caused by low factor VIII levels. PT and platelet count will be normal.

KEY FACT

ASA ↑ the risk for bleeding in patients with vWD.

Treatment

- **Best initial treatment:** Desmopressin for mild to moderate disease to release the endogenous vWF from storage sites in endothelial cells. For more severe disease, for major bleeds and surgery, and for those who do not respond to desmopressin such as type 2 vWD, patients should receive replacement therapy of vWF/factor VIII concentrates.
- Antifibrinolytic agents such as aminocaproic acid and tranexamic acid can be used as

adjunct treatment for bleeding from mucosal sites such as the nose, oropharynx, and urogenital tract.

- Control menorrhagia with oral contraceptive pills (OCPs). Drugs to be avoided are ASA, nonsteroidal anti-inflammatory drugs (NSAIDs), and platelet function inhibitors.

KEY FACT

VWD types 1 and 2 are generally inherited in an autosomal dominant pattern. VWD type 3 is inherited in an autosomal recessive pattern.

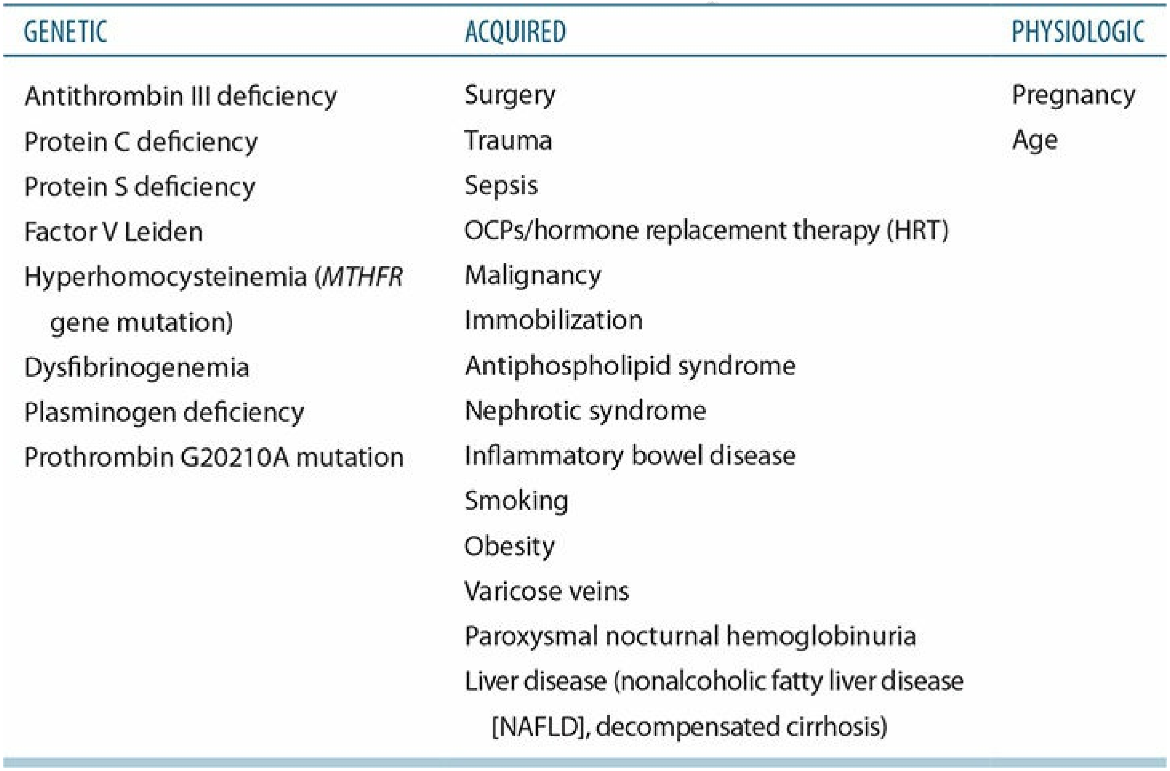
HYPERCOAGULABLE STATES

Hypercoagulable states (thrombophilias or prothrombotic states) are an all-inclusive term describing conditions that ↑ a patient's risk for developing thrombosis, usually venous thromboembolism (VTE) disease.

Etiology

Etiologies can be genetic, acquired, or physiologic (see Table 2.7-6).

TABLE 2.7-6. Causes of Hypercoagulable States



GENETIC	ACQUIRED	PHYSIOLOGIC
Antithrombin III deficiency	Surgery	Pregnancy
Protein C deficiency	Trauma	Age
Protein S deficiency	Sepsis	
Factor V Leiden	OCPs/hormone replacement therapy (HRT)	
Hyperhomocysteinemia (*MTHFR* gene mutation)	Malignancy	
	Immobilization	
Dysfibrinogenemia	Antiphospholipid syndrome	
Plasminogen deficiency	Nephrotic syndrome	
Prothrombin G20210A mutation	Inflammatory bowel disease	
	Smoking	
	Obesity	
	Varicose veins	
	Paroxysmal nocturnal hemoglobinuria	
	Liver disease (nonalcoholic fatty liver disease [NAFLD], decompensated cirrhosis)	

History/PE

Thrombophilias can present with recurrent thrombotic complications: deep venous thrombosis (DVT), pulmonary embolism, arterial thrombosis, myocardial infarction (MI), and stroke. Females may have recurrent miscarriages.

Diagnosis

- Ruling out acquired causes of thrombosis before thrombophilia screening such as immobilization, surgery, OCPs, pregnancy, and hormone replacement therapy
- **Thrombophilia screening:** To be considered only in patients with a history of VTE in the absence of risk factors and in patients with a first-degree relative who had VTE at <50 years of age or a first-degree relative with a diagnosis of thrombophilia
- Hereditary abnormality confirmed with two abnormal values obtained while the patient is asymptomatic and untreated, with similar values obtained in two other family members
- **Lab tests:** Complete blood count (CBC), PT, thrombin time, PTT, fibrinogen, and assays for antithrombin and protein C and S deficiency

Treatment

- Patients with a hypercoagulable state with a provoked DVT or pulmonary embolism can be treated with heparin, low-molecular-weight heparin (LMWH), warfarin, or a DOAC for 3 to 6 months for the first VTE event and lifelong anticoagulation for subsequent events.
- If anticoagulation is contraindicated (eg, recent trauma, hemorrhage, severe uncontrolled hypertension) or if patients have recurrent DVTs on therapeutic doses of anticoagulation, an inferior vena cava filter is the next best step.

ACTIVATED PROTEIN C (APC) RESISTANCE/FACTOR V LEIDEN

The most common cause of inherited thrombophilia. A single-point mutation in factor V, rendering it resistant to being inactivated/broken down by activated protein C. Risk for DVT or pulmonary embolism is ↑ 5-fold if heterozygous and 50-fold if homozygous.

KEY FACT

Protein C or S deficiency: Hypercoagulable state with skin or tissue necrosis following warfarin administration

History/PE

Factor V Leiden: Young, White patients (<45 years of age) with a personal and family history of thrombosis (eg, multiple VTEs, unusual location, atypically young age)

Diagnosis

Disease-specific tests: Factor V Leiden (APC resistance test) functional assay or genetic testing

KEY FACT

The liver is responsible for the synthesis of proteins C and S. In cases of decompensated cirrhosis, deficiency in protein C and S can cause a hypercoagulable state.

Treatment

Factor V Leiden mutation: Direct oral anticoagulation without the need of monitoring INR. Can use warfarin for 6 months with a target INR of 2 to 3 in patients who trigger concerns about compliance with medication, in individuals taking medications that can interact with direct oral anticoagulants (DOACs), or in individuals who have extreme body weight due to erratic absorption. OCPs should be avoided in patients with factor V Leiden.

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

A drop in platelet count more commonly observed due to unfractionated heparin (UFH) than to LMWH. It can happen with heparin or enoxaparin.

- **HIT type I:** A mild, nonimmune-mediated transient decrease in platelet count that occurs 1 to 4 days after heparin initiation. The platelet nadir is typically ~100 k/μL This type of HIT is benign and requires only observation. No heparin interruption is required.
- **HIT type II:** An immunologic reaction due to the formation of platelet-activating antibodies against heparin-prostaglandin (PG)4 antigen, which leads to the formation of blood clots and a drop in platelet count. It is usually a severe and rapid (>50%) drop in platelet count that occurs 5 to 10 days after starting heparin. HIT type II often presents as skin necrosis at the injection site of subcutaneous heparin. HIT rarely causes bleeding. Venous and arterial thromboses can occur; however, VTEs are more common. Heparin discontinuation is required, and a nonheparin anticoagulant must be initiated.

KEY FACT

Pulmonary embolism should be suspected in a patient with rapid onset of dyspnea, pleuritic chest pain, hypoxia, tachycardia, and an ↑ alveolar-arterial oxygen gradient without another obvious explanation.

Diagnosis

- The **4Ts score** helps differentiate thrombocytopenia due to HIT from other causes. This score includes the platelet count fall (**T**hrombocytopenia), the **T**iming of platelet count fall, evidence of **T**hrombosis or skin necrosis, and the probability of other causes for the **T**hrombocytopenia.
- **Disease-specific tests:**
  - **Best initial test:** Evidence of the HIT platelet factor 4 antibody
  - **Most accurate test:** Functional assay with the serotonin release assay

MNEMONIC

Antiphospholipid syndrome effects—

CLOTS

Coagulation defect
Livedo reticularis
Obstetric (recurrent miscarriage)
Thrombocytopenia (↓ platelets)
SLE (association)

Treatment

Discontinuing heparin immediately upon suspicion of diagnosis and starting a direct thrombin inhibitor (eg, fondaparinux, argatroban, and bivalirudin). Warfarin should be commenced after a direct thrombin inhibitor is started and once platelet count is >150,000. Starting nonheparin anticoagulation is crucial to prevent arterial and venous clots.

Q 1

A 65-year-old male was recently admitted to the hospital for management of a DVT with heparin. Two days after his admission, he was found to have petechiae. Laboratory testing identified a drop in platelet count from 180,000 to 50,000. What is the best next step in management of his thrombo-cytopenia?

Q 2

A 33-year-old woman was admitted to the hospital for anticoagulation after a pulmonary embolism. On day 4 of her stay, her platelet level ↓ from 150,000 to 60,000/mm_3, and her INR remains <2. What is the next best step, and what complications can result from this condition?

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is often associated with systemic lupus erythematosus (SLE) (20%–30%) and rheumatoid arthritis (RA). The main APS antibodies are the lupus anticoagulant, anti-beta-2-glycoprotein, and anticardiolipin. APS predisposes to both arterial and venous thrombi formation and spontaneous abortion (particularly associated with anticardiolipin antibodies). Laboratory testing shows a paradoxically prolonged PTT (only thrombophilia with an abnormality in the PTT).

History/PE

APS: Most commonly in young and middle-aged females with recurrent miscarriages or thrombosis. Could have a history suggestive of SLE with photosensitivity, oral ulcers, patchy hair loss, and Raynaud phenomenon.

Diagnosis

Diagnostic criteria for APS (at least one clinical and one laboratory criterion need to be met):

- **Clinical criteria:**
  - Evidence of vascular thrombosis events
- Any of the following pregnancy complications:
  1. ≥1 spontaneous abortion of a normal fetus at or beyond 10 weeks gestational age (GA)
  2. ≥1 premature births of a morphologically normal neonate before 34 weeks GA
  3. Three or more unexplained consecutive spontaneous abortions before 10 weeks GA unexplained by any maternal or paternal causes (anatomic, chromosomal or hormonal)
- **Laboratory criteria:** Detection of lupus anticoagulant or anti-beta-2 glycoprotein I antibody or anticardiolipin antibody on two or more occasions, at least 2 weeks apart.

Laboratory testing showing a paradoxically prolonged PTT and normal PT. PTT does not correct with a mixing study due to the presence of antibodies. The addition of excess phospholipids can correct the prolonged PTT.

Disease-specific tests for APS: Lupus anticoagulant and anticardiolipin antibodies.

Treatment

- For vascular events, treatment with LMWH or UFH and bridge to warfarin until the INR is in the therapeutic range. May require lifelong anticoagulation with warfarin. DOACs are less effective in APS.
- Thromboprophylaxis is controversial in APS in the absence of vascular events.

KEY FACT

In patients with recent exposure to warfarin who are experiencing warfarin-induced skin necrosis, the physician should suspect protein C or S deficiency.

DISSEMINATED INTRAVASCULAR COAGULATION

An acquired coagulopathy caused by deposition of fibrin in small blood vessels, leading to thrombosis and end-organ damage. Depletion of clotting factors and platelets leads to a bleeding diathesis. It is associated with many severe illnesses and is often seen in hospitalized patients.

Disseminated intravascular coagulation (DIC) can be acute or chronic.

KEY FACT

DIC is characterized by both thrombosis and hemorrhage.

1 A

This patient has HIT type I. The best next step is to discontinue heparin immediately and treat the DVT with a direct thrombin inhibitor.

2 A

This patient is experiencing HIT, which occurs secondary to the formation of antibodies that activate platelets. Because HIT can lead to a hypercoagulable state and subsequent thrombotic complications, heparin must be stopped immediately, and the patient must be switched to argatroban, bivalirudin, or fondaparinux.

History/PE

Some common causes of DIC can be found in Table 2.7-7.

TABLE 2.7-7. **Common Etiologies for DIC**

Obstetric complications (eg, amniotic fluid embolism, abruptio placentae)	Vascular disorders (aortic aneurysm)
Malignancy (acute promyelocytic leukemia, pancreatic cancer)	Systemic disorders: sepsis, transfusion reactions, transplant rejections, hemolysis, drug reactions, acidosis
Acute respiratory distress syndrome (ARDS), pancreatitis, burns	Other: massive trauma, snake bites

Clinical presentation:

- **Acute DIC** is observed with a recent history of trauma or sepsis or in patients with a history of ABO-incompatible blood transfusions. It presents with bleeding; low platelet count and plasma fibrinogen; and a prolonged PT, PTT, and D-dimer.
    - Presents with shock and multiorgan dysfunction (renal dysfunction, hepatic dysfunction, and transient neurologic syndromes). Bleeding from venipuncture sites into organs, with ecchymoses and petechiae.
- **Chronic DIC** is observed in patients with a chronic history of cancer; normal to low platelet count; normal to mildly high PT, PTT, and fibrinogen; and elevated D-dimer. It is often asymptomatic and can present with laboratory changes only. It can also present with venous or arterial thromboembolism without an identifiable precipitating factor.

KEY FACT

DIC is characterized by both thrombosis and hemorrhage.

Diagnosis

- **Lab tests:** ↑ PT and PTT, ↓ platelets (thrombocytopenia), ↑ d-dimer and fibrin, ↓ fibrinogen.
- Possibility for DIC to be confused with liver disease. Unlike liver disease, factor VIII is depressed in DIC.

Treatment

Treatment of the underlying cause; transfusion of RBCs, platelets, and fresh frozen plasma (FFP); and management of shock as necessary.

PLATELET DISORDERS

THROMBOTIC THROMBOCYTOPENIC PURPURA

Thrombotic thrombocytopenic purpura (TTP) is a deficiency of the vWF-cleaving enzyme (ADAMTS-13), resulting in abnormally large vWF multimers that aggregate platelets and create platelet microthrombi. These block small blood vessels, leading to end-organ damage.

RBCs are fragmented by contact with the microthrombi, leading to hemolysis (microangiopathic hemolytic anemia) and thrombocytopenia. TTP is a medical emergency and can be immune-mediated or hereditary.

History/PE

TTP: Associated with SLE, malignancy, pregnancy, cyclosporine, quinidine, clopidogrel, ticlopidine, and AIDS. TTP can also be hereditary. Classic description involves a pentad of features. The physician should suspect TTP if three of five of the following symptoms are present **(LMNOP):**

1. **L**ow platelet count (thrombocytopenia)
2. **M**icroangiopathic hemolytic anemia with schistocytes (severe, often with jaundice)
3. **N**eurologic changes (delirium, seizure, stroke, ↓ consciousness, ↓ vision)
4. "**O**bsolete" (impaired) renal function (acute kidney injury [AKI])
5. **P**yrexia (fever)

Diagnosis

General workup for thrombocytopenia can be found in Figure 2.7-4.

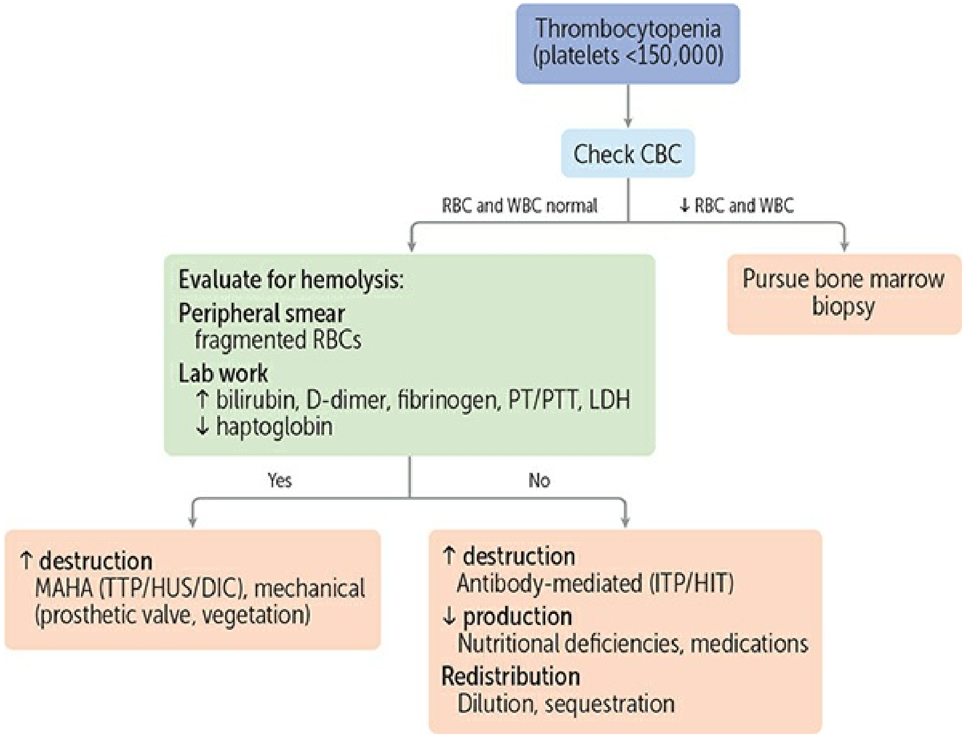

Thrombocytopenia (platelets <150,000)
Check CBC
RBC and WBC normal
↓ RBC and WBC
Evaluate for hemolysis:
Peripheral smear
fragmented RBCs
Lab work
↑ bilirubin, D-dimer, fibrinogen, PT/PTT, LDH
↓ haptoglobin
Pursue bone marrow biopsy
Yes
No
↑ destruction
MAHA (TTP/HUS/DIC), mechanical (prosthetic valve, vegetation)
↑ destruction
Antibody-mediated (ITP/HIT)
↓ production
Nutritional deficiencies, medications
Redistribution
Dilution, sequestration

FIGURE 2.7-4. **Thrombocytopenia workup.** (Reproduced with permission from USMLE-Rx.com.)

- **Lab tests:** ↓ platelets, ↓ hemoglobin (Hb), ↑ creatinine, normal clotting/coagulation screen. PT, PTT, and fibrinogen are normal, which is different from the coagulation profile observed in DIC.
- In addition, due to the hemolysis, lactate dehydrogenase (LDH) and indirect bilirubin are increased, while haptoglobin is decreased.
- **Blood film:** Presence of schistocytes (fragmented RBCs) (see Fig. 2.7-5)

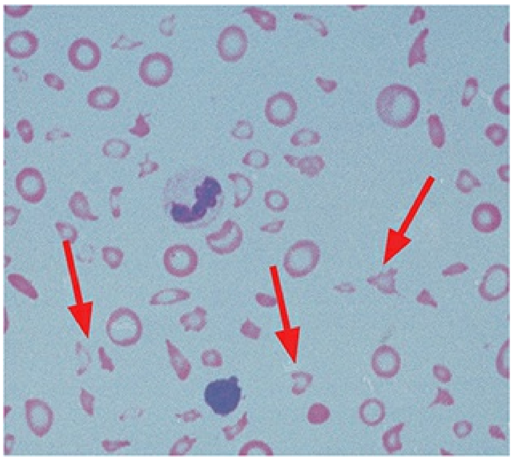


FIGURE 2.7-5. **Schistocytes.** These fragmented RBCs *(arrows)* can be seen in microangiopathic hemolytic anemia and in mechanical hemolysis such as that due to an artificial heart valve. (Reproduced with permission from Dr. Peter McPhedran, Yale Department of Hematology.)

- **Most accurate diagnostic test:** Measurement of ADAMTS-13 activity

Treatment

- **TTP:** Plasma exchange is the best initial treatment. Steroids and rituximab can be added to ↓ microthrombus formation.
- Platelet transfusion is contraindicated in TTP, as additional platelets are consumed by the disease process, potentially worsening the patient's condition.

HEMOLYTIC UREMIC SYNDROME

Hemolytic uremic syndrome (HUS) and TTP have overlapping clinical manifestations and are considered a spectrum of the same disease that is caused by ADAMTS-13 deficiency, which is either inherited or often acquired secondary to infection. TTP is more common in adults, and HUS is frequently seen in children (associated with *Escherichia coli* 0157:H7).

HUS: Can present similarly to TTP with the absence of neurologic features.

- >90% of cases in children are caused by *E coli* O157:H7 hemorrhagic diarrhea, which precedes the syndrome. The *E coli* infection is triggered by eating undercooked, contaminated meat.
- Characterized by renal failure, microangiopathic hemolytic anemia, and low platelets *without* neurologic symptoms.
- Abdominal pain, bloody diarrhea, and AKI often seen. Severe ↑ in creatinine levels is more typical of HUS than of TTP.
- Schistocytes (fragmented RBCs) seen in both HUS and TTP.

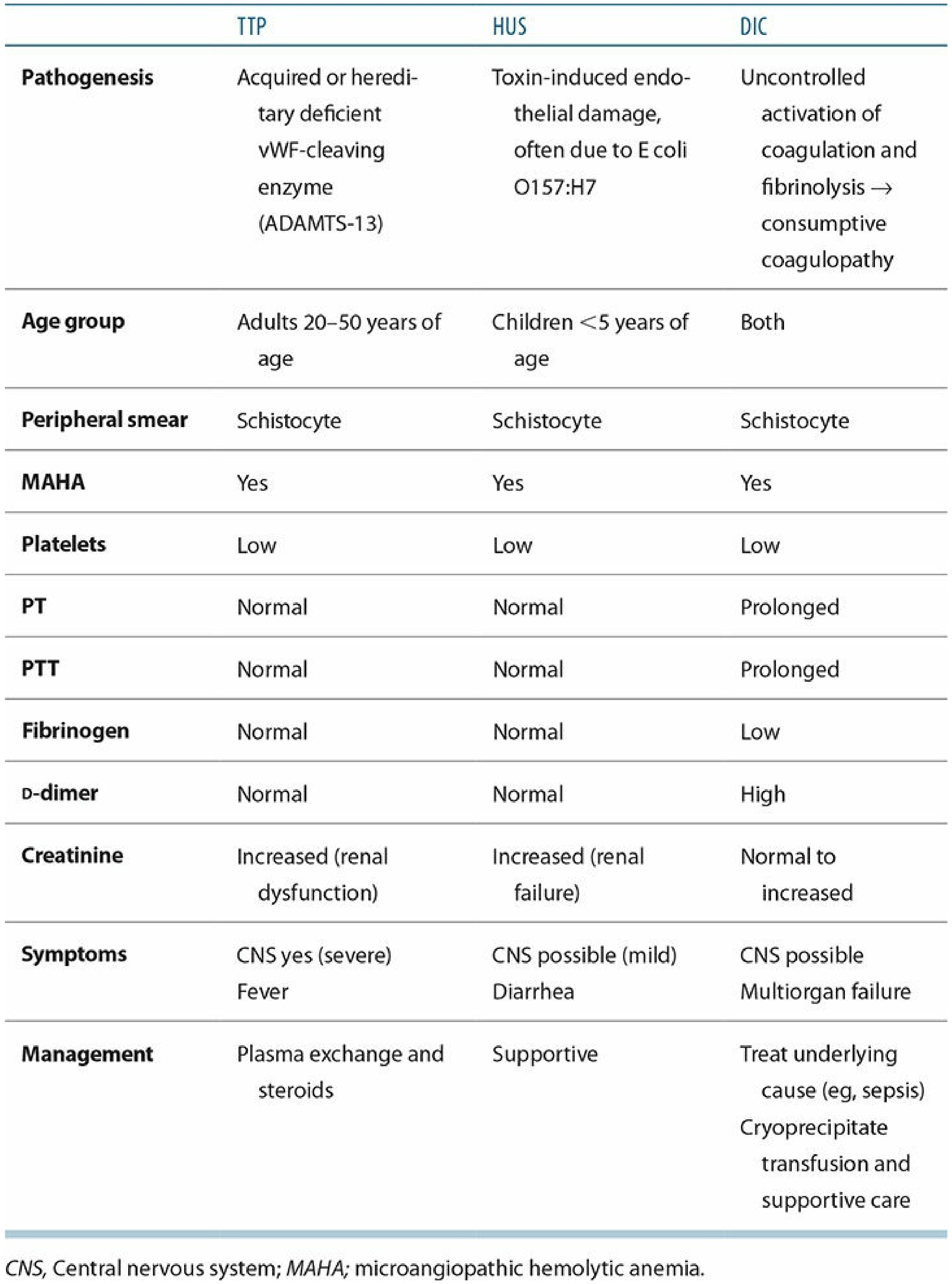
Diagnosis

- **Lab tests:** ↓ platelets, ↓ Hb, ↑ creatinine, normal clotting/coagulation screen. PT, PTT, and fibrinogen are normal, which is different from the coagulation profile observed in DIC.
- In addition, due to the hemolysis, LDH and indirect bilirubin are increased, whereas haptoglobin is decreased.
- **Blood film:** Presence of schistocytes (fragmented RBCs) (see Fig. 2.7-5).

Treatment

- **HUS:** Dialysis for AKI may be needed. Plasma exchange is used for severe, persistent disease. Antibiotics and antimotility drugs such as anticholinergics are not recommended, as they have been shown to increase the likelihood of HUS resulting from *E coli* O157:H7.
- One other key point is that hydration can help reduce the risk of AKI.
- Platelet transfusion is contraindicated in HUS, as additional platelets are consumed by the disease process, potentially worsening the patient's condition.
- A summary of the clinical and laboratory findings seen in TTP, HUS and DIC can be found in Table 2.7-8 and the common laboratory features seen in different bleeding disorders can be seen in Table 2.7-9.

TABLE 2.7-8. Summary of the Clinical and Laboratory Features of TTP, HUS, and DIC



	TTP	HUS	DIC
Pathogenesis	Acquired or hereditary deficient vWF-cleaving enzyme (ADAMTS-13)	Toxin-induced endothelial damage, often due to E coli O157:H7	Uncontrolled activation of coagulation and fibrinolysis → consumptive coagulopathy
Age group	Adults 20–50 years of age	Children <5 years of age	Both
Peripheral smear	Schistocyte	Schistocyte	Schistocyte
MAHA	Yes	Yes	Yes
Platelets	Low	Low	Low
PT	Normal	Normal	Prolonged
PTT	Normal	Normal	Prolonged
Fibrinogen	Normal	Normal	Low
D-dimer	Normal	Normal	High
Creatinine	Increased (renal dysfunction)	Increased (renal failure)	Normal to increased
Symptoms	CNS yes (severe) Fever	CNS possible (mild) Diarrhea	CNS possible Multiorgan failure
Management	Plasma exchange and steroids	Supportive	Treat underlying cause (eg, sepsis) Cryoprecipitate transfusion and supportive care

CNS, Central nervous system; *MAHA;* microangiopathic hemolytic anemia.

TABLE 2.7-9. **Laboratory Features of Bleeding Disorders**

	THROMBOCYTOPENIA	VWD	HEMOPHILIA	VITAMIN K DEFICIENCY	LIVER DISEASE	DIC
Platelet count	Low	Normal	Normal	Normal	Low to normal	Low
Bleeding time	Prolonged	Prolonged	Normal	Normal	Normal	Prolonged
PT	Normal	Normal	Normal	Prolonged	Prolonged	Prolonged
PTT	Normal	Normal to prolonged	Prolonged	Prolonged	Prolonged	Prolonged
Fibrinogen	Normal	Normal	Normal	Normal	Normal	Low
D-dimer	Normal	Normal	Normal	Normal	Normal	High

Q

An 8-year-old girl presents to the emergency department with 2 days of fever, vomiting, bloody diarrhea, and irritability. She began feeling unwell after attending a classmate's birthday party. Laboratory results reveal thrombocytopenia, ↑ creatinine level, and schistocytes. What is the next best step?

IDIOPATHIC THROMBOCYTOPENIC PURPURA (IMMUNE THROMBOCYTOPENIA)

IgG antibodies are formed against the membrane protein Gp Iib/IIIa of platelets. The platelet-antibody complex is destroyed by the spleen. Bone marrow production of platelets is ↑, with ↑ megakaryocytes in the marrow. It is the most common immunologic disorder in females of childbearing age.

History/PE

- Patients often feel well with no systemic symptoms. They may have minor mucocutaneous bleeding, easy bruising, petechiae, hematuria, or melena. Generally there is no splenomegaly. (Splenomegaly can also cause platelet sequestration resulting in thrombocytopenia, generally seen in myeloproliferative disorders, infections like malaria, and visceral leishmaniasis.)
- Idiopathic thrombocytopenic purpura (ITP) is associated with a range of conditions, including malignancies (lymphoma, leukemia), autoimmune disorders (SLE), and viral infections (HIV, hepatitis C virus [HCV]). It can present acutely or as a chronic illness.
- Acute: Abrupt onset of hemorrhagic complications occurs after a viral illness with sudden, self-limiting purpura. It commonly affects children 2 to 6 years of age, with boys and girls affected equally.
- Chronic: Insidious onset of symptoms occurs, or CBC shows incidental thrombocytopenia. There is a fluctuating course of bleeding, purpura, epistaxis, and menorrhagia. It affects adults 20 to 40 years of age and females more than males.

A

HUS is the most common cause of acute renal failure in children. Supportive therapy includes intravenous (IV) fluids, blood pressure (BP) control, blood transfusion, and, if necessary, dialysis. Antibiotics are not indicated, as they are thought to ↓ expulsion of the toxin and may ↑ toxin from the destruction of bacteria.

Diagnosis

- The diagnosis is one of exclusion. Once other causes of thrombocytopenia have been ruled out, diagnosis can occur via history and PE, a CBC, and a peripheral blood smear showing megakaryocytes and normal RBC morphology.
  - It is important to rule out pseudothrombocytopenia due to platelet clumping by ethylenediaminetetraacetic acid (EDTA) in test tubes.
- Antiplatelet antibodies are often present.
- Bone marrow biopsy would also show ↑ megakaryocytes but is done only in atypical cases or patients >60 years of age.
- Additional tests for all patients with ITP include HIV (5%–10% of chronic HIV patients may present with isolated thrombocytopenia), hepatitis C, *Helicobacter pylori*, direct antiglobulin test, and blood type.

KEY FACT

Anti-D (Rh) immunoglobulin and rituximab are second-line therapies for ITP. Anti-D (Rh) immunoglobulin and IVIG act as “decoys” so that WBCs will recognize them instead of IgG on platelets.

Treatment

- Platelet count >30,000 and no bleeding: No treatment required
- Platelet count <30,000 or clinically significant bleeding symptoms: Corticosteroids or intravenous immunoglobulin (IVIG)
- If platelet count fails to improve or bleeding recurs, the physician should consider splenectomy ± rituximab ± thrombopoietin (TPO) receptor agonist to ↑ platelet production (romiplostim or eltrombopag).
- Platelet transfusions are not used (except during splenectomy or life-threatening hemorrhage), as the platelets are quickly destroyed by autoantibodies.
- If caused by HCV or HIV, treatment of the underlying infection can improve platelet count.
- In pregnant patients, severe thrombocytopenia may occur in the fetus.

KEY FACT

Steroid-sparing therapies are generally agents used as alternatives to avoid steroid-related adverse events such as high blood sugar and osteoporosis.

RED BLOOD CELL DISORDERS

ANEMIAS

Disorders of low hematocrit (Hct) and Hb. Subtypes are classified according to RBC mean corpuscular volume (MCV) and reticulocyte count (see Fig. 2.7-6).

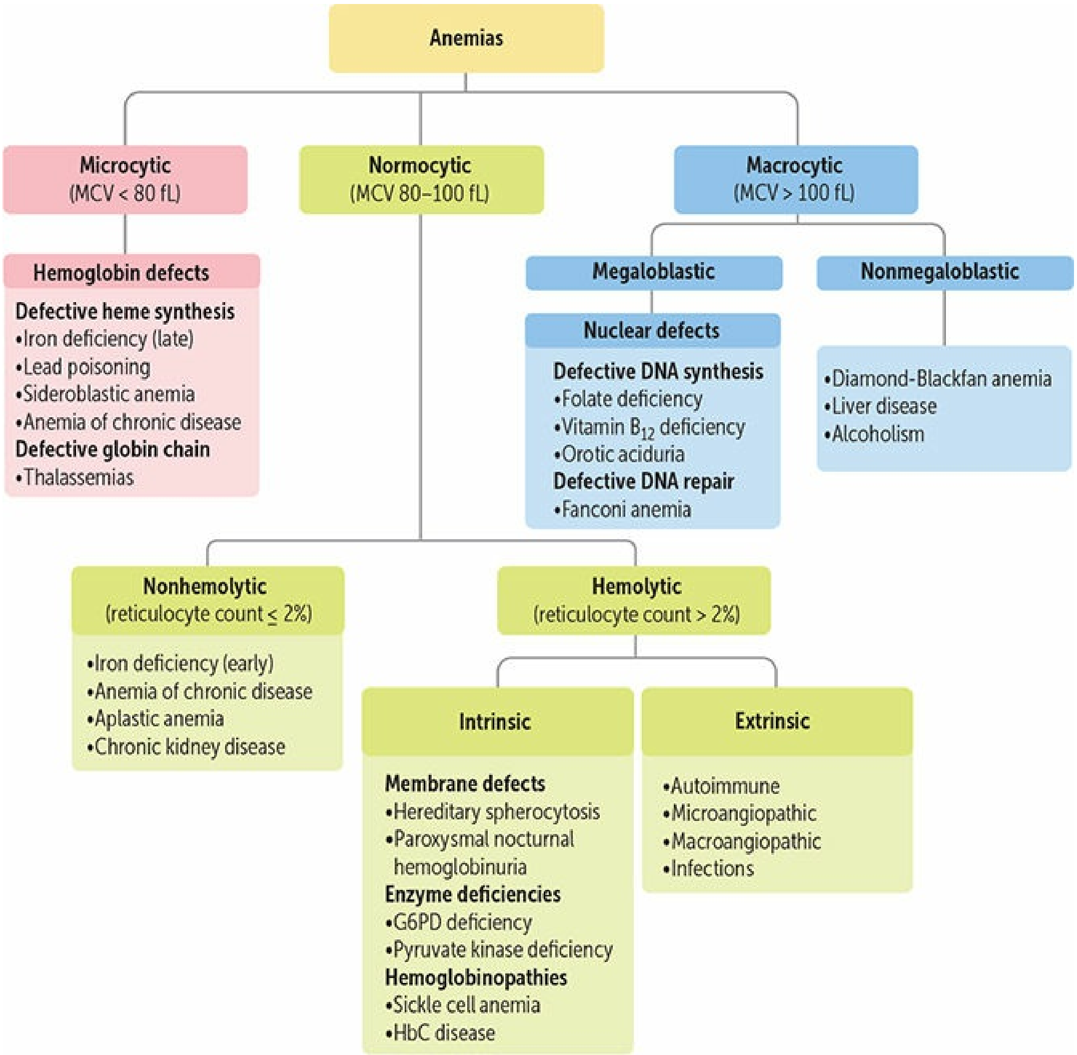

Anemias
Microcytic
(MCV < 80 fL)
Normocytic
(MCV 80–100 fL)
Macrocytic
(MCV > 100 fL)
Hemoglobin defects
Defective heme synthesis
•Iron deficiency (late)
•Lead poisoning
•Sideroblastic anemia
•Anemia of chronic disease
Defective globin chain
•Thalassemias
Megaloblastic
Nonmegaloblastic
Nuclear defects
Defective DNA synthesis
•Folate deficiency
•Vitamin B12 deficiency
•Orotic aciduria
Defective DNA repair
•Fanconi anemia
•Diamond-Blackfan anemia
•Liver disease
•Alcoholism
Nonhemolytic
(reticulocyte count ≤ 2%)
•Iron deficiency (early)
•Anemia of chronic disease
•Aplastic anemia
•Chronic kidney disease
Hemolytic
(reticulocyte count > 2%)
Intrinsic
Membrane defects
•Hereditary spherocytosis
•Paroxysmal nocturnal hemoglobinuria
Enzyme deficiencies
•G6PD deficiency
•Pyruvate kinase deficiency
Hemoglobinopathies
•Sickle cell anemia
•HbC disease
Extrinsic
•Autoimmune
•Microangiopathic
•Macroangiopathic
•Infections

FIGURE 2.7-6. **Anemia algorithm.** (Reproduced with permission from USMLE-Rx.com.)

MICROCYTIC ANEMIAs

Iron Deficiency Anemia

Occurs due to ↑ demand (eg, growing period, pregnancy, erythropoietin [EPO] therapy) or ↓ iron due to chronic bleeding (menorrhagia, GI loss), malnutrition/absorption disorders (eg, celiac disease), and GI surgery (eg, gastrectomy). Toddlers, adolescent females, and females of reproductive age constitute high-risk groups.

KEY FACT

Microcytic anemias, or microcytosis, have a low MCV (<80 Fl) and generally have a low reticulocyte count.

History/PE

- **Symptoms:** Fatigue, dyspnea, tachycardia, angina, syncope, and pica (persistent craving and compulsive eating of nonfood substances).
- **Physical findings:** Glossitis, cheilosis, conjunctival pallor, and koilonychia (“spoon nails,” see Fig. 2.7-7), Plummer-Vinson syndrome (triad of iron deficiency anemia,

esophageal webs, and dysphagia).

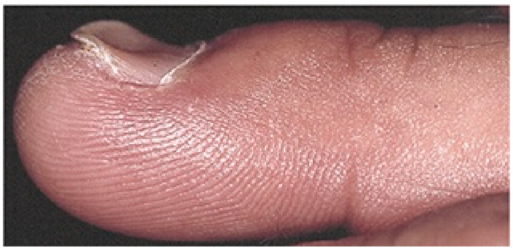
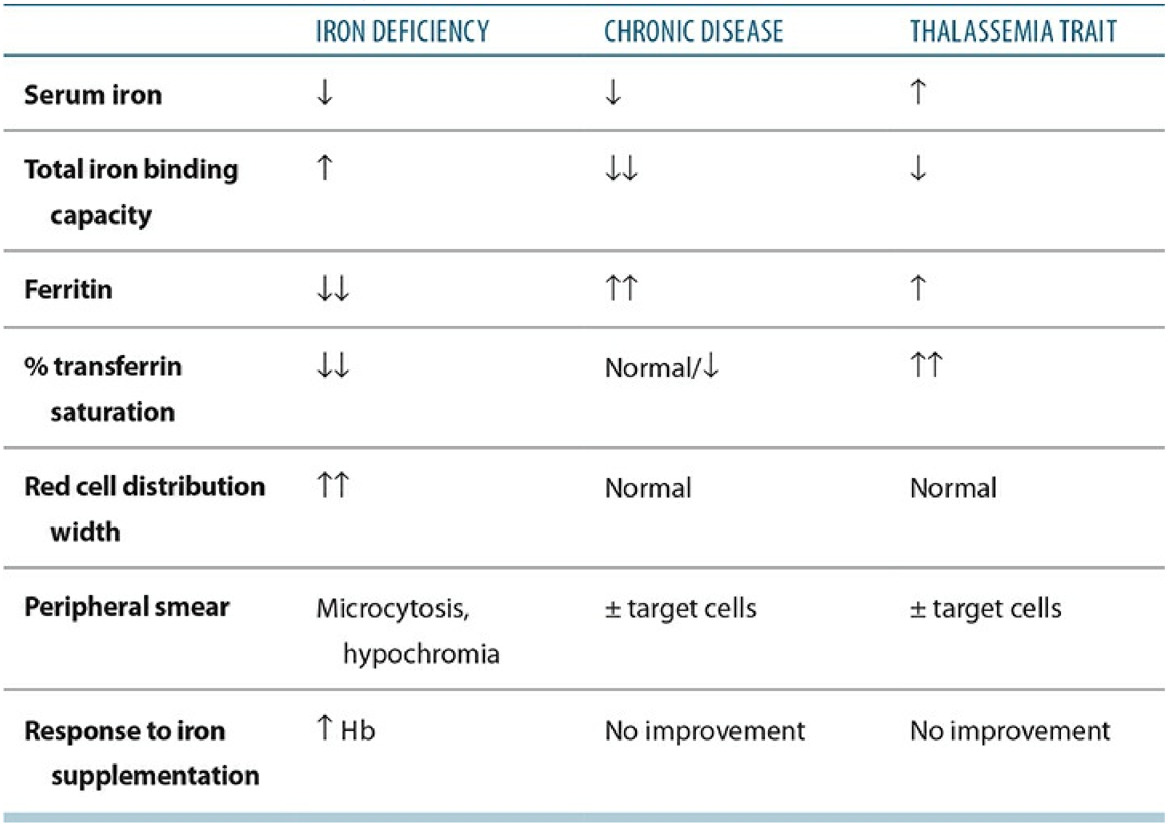


FIGURE 2.7-7. **Koilonychia (spoon nails).** The fingernail plate is concave. (Reproduced with permission from Wolff K, et al. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*. New York, NY: McGraw-Hill; 2013.)

Diagnosis

- **Best initial test:** CBC (↓ MCV, ↓ mean corpuscular Hb [MCH], ↓ mean corpuscular Hb concentration [MCHC]) with iron profile (see Table 2.7-10). Iron deficiency anemia should be distinguished from thalassemia and anemia of chronic disease.

TABLE 2.7-10. **Iron Deficiency Anemia vs Anemia of Chronic Disease vs. Thalassemia**



	IRON DEFICIENCY	CHRONIC DISEASE	THALASSEMIA TRAIT
Serum iron	↓	↓	↑
Total iron binding capacity	↑	↓↓	↓
Ferritin	↓↓	↑↑	↑
% transferrin saturation	↓↓	Normal/↓	↑↑
Red cell distribution width	↑↑	Normal	Normal
Peripheral smear	Microcytosis, hypochromia	± target cells	± target cells
Response to iron supplementation	↑ Hb	No improvement	No improvement

- **Most accurate test:** Bone marrow iron stain (Prussian blue stain).
- Peripheral blood smear can show microcytic, hypochromic RBCs (see Fig. 2.7-8) with anisocytosis, poikilocytosis, and a low reticulocyte count.

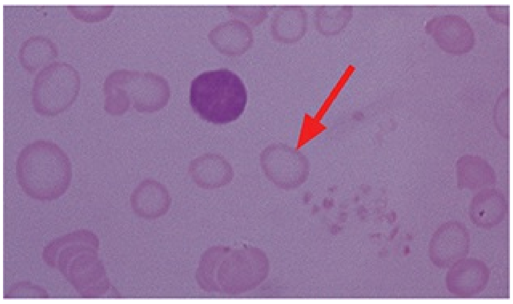


FIGURE 2.7-8. **Iron deficiency anemia.** Note the microcytic, hypochromic RBCs ("doughnut cells") with enlarged areas of central pallor *(arrow).* (Reproduced with permission from Dr. Peter McPhedran, Yale Department of Hematology.)

KEY FACT

Iron deficiency anemia in an older adult patient may be caused by colorectal cancer until proven otherwise and must therefore be evaluated to rule out malignancy.

MNEMONIC

Causes of microcytic anemia—

IRON LAST

IRON deficiency
Lead poisoning
Anemia of chronic disease
Sideroblastic anemia
Thalassemia

Treatment

- Iron supplementation. Oral iron is preferred over IV iron. Duration of oral iron replacement to replenish stores depends on iron deficit (6 weeks to 6 months).
- Oral iron may lead to nausea, constipation, diarrhea, abdominal pain, and black stools. Alternate-day therapy can minimize GI adverse effects. Antacids may interfere with iron absorption.
- IV iron is preferred if the oral route is ineffective (eg, gluten sensitivity, inflammatory bowel disease, GI malabsorption, post–gastric bypass surgery, hyperemesis gravidarum, and a history of oral iron intolerance).
- IV iron is superior to oral iron in achieving a sustained Hb response; reducing the need for packed RBC transfusions; and improving the quality of life for patients with chronic heart failure, inflammatory bowel disease, chronic kidney disease and hemodialysis, and cancer-related anemia.
- IV iron dextran is associated with a small risk for serious adverse effects, including anaphylaxis. Iron sucrose may be associated with a lower risk for allergy.

KEY FACT

Anemia secondary to end-stage renal disease is caused by deficiency of EPO. Treatment with recombinant EPO is effective but often leads to worsening of hypertension.

Anemia of Chronic Inflammation/Disease

To limit bacterial proliferation, the body "hides" or "locks" its iron in situations of chronic inflammation such as infection, malignancy, RA, or SLE. Iron is trapped in macrophages or in ferritin (↑ in inflammation). This results in a microcytic or normocytic anemia with normal or ↑ levels of iron storage in the form of ferritin but ↓ serum iron and ↓ total iron binding capacity (TIBC) (see Table 2.7-4). Treatment consists of treating the underlying disease. Anemia associated with end-stage renal disease (ESRD) responds to EPO replacement, once iron stores have been repleted.

Lead Poisoning

Inhibits ferrochelatase and δ-aminolevulinic acid (ALA) dehydratase → ↓ heme synthesis and ↑ RBC protoporphyrin. Also inhibits ribosomal RNA (Rrna) degradation → RBCs retain aggregates of Rrna (basophilic stippling). Exposure risk ↑ in adults because of inhalation during industrial work (battery factory) and in children because of eating lead paint (old houses with chipped paint built before 1978).
History/PE: Symptoms of **LEAD** poisoning include:

- **L**ead **L**ines on gingivae (Burton lines) and on metaphyses of long bones on x-ray
- **E**ncephalopathy and **E**rythrocyte basophilic stippling
- **A**bdominal pain (lead colic) and sideroblastic **A**nemia
- **D**rops—wrist and foot drops

Labs: ↓ Hb, ↓ MCV
Treatment: Removal from the exposure, chelation with succimer, EDTA, dimercaprol

Sideroblastic Anemia

- Occurs due to defective heme synthesis.
- **Causes:** Genetic (eg, X-linked defect in ALA synthase gene); acquired (myelodysplastic syndromes); and reversible (alcohol is most common and can suppress bone marrow; also lead poisoning, vitamin B_6 deficiency, copper deficiency, drugs [eg, isoniazid, linezolid]).
- ***Hx/PE/Labs:*** Presents with ↓ Hb, ↓ MCV. Iron studies show iron overload (↑ serum iron, normal/↓ TIBC, ↑ ferritin). Peripheral blood smear shows basophilic stippling of RBCs (in lead poisoning).
- ***Dx:*** Presence of ringed sideroblasts (with iron-laden, Prussian blue–stained mitochondria) on bone marrow smear is diagnostic (see Fig. 2.7-9).

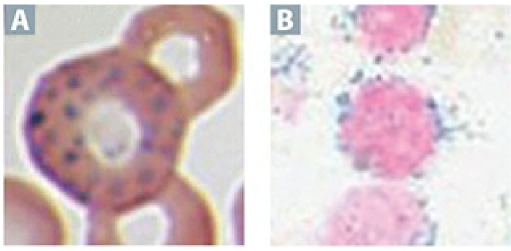


FIGURE 2.7-9. **Pathogenic RBC forms. (A)** Basophilic stippling. **(B)** Ringed sideroblasts.
(Image A reproduced courtesy of van Dijk HA, Fred HL. Images of memorable cases: case 81. OpenStax website. June 18, 2018. Available at https://cnx.org/contents/57cfLKUe@7.2:MZa_Ph4e@4/Images-of-Memorable-Cases-Case. Image B reproduced with permission from Invernizzi R, Quaglia F, Porta MG. Importance of classical morphology in the diagnosis of myelodysplastic syndrome. Mediterr J Hematol Infect Dis. 2015 May 1;7(1):e2015035. doi: 10.4084/MJHID.2015.035.)

- ***Tx:*** Treatment of the underlying cause. Treatment of acquired causes with pyridoxine (vitamin B_6, cofactor for ALA synthase).

KEY FACT

Sideroblastic anemia is the only form of microcytic anemia in which the serum iron level is elevated.

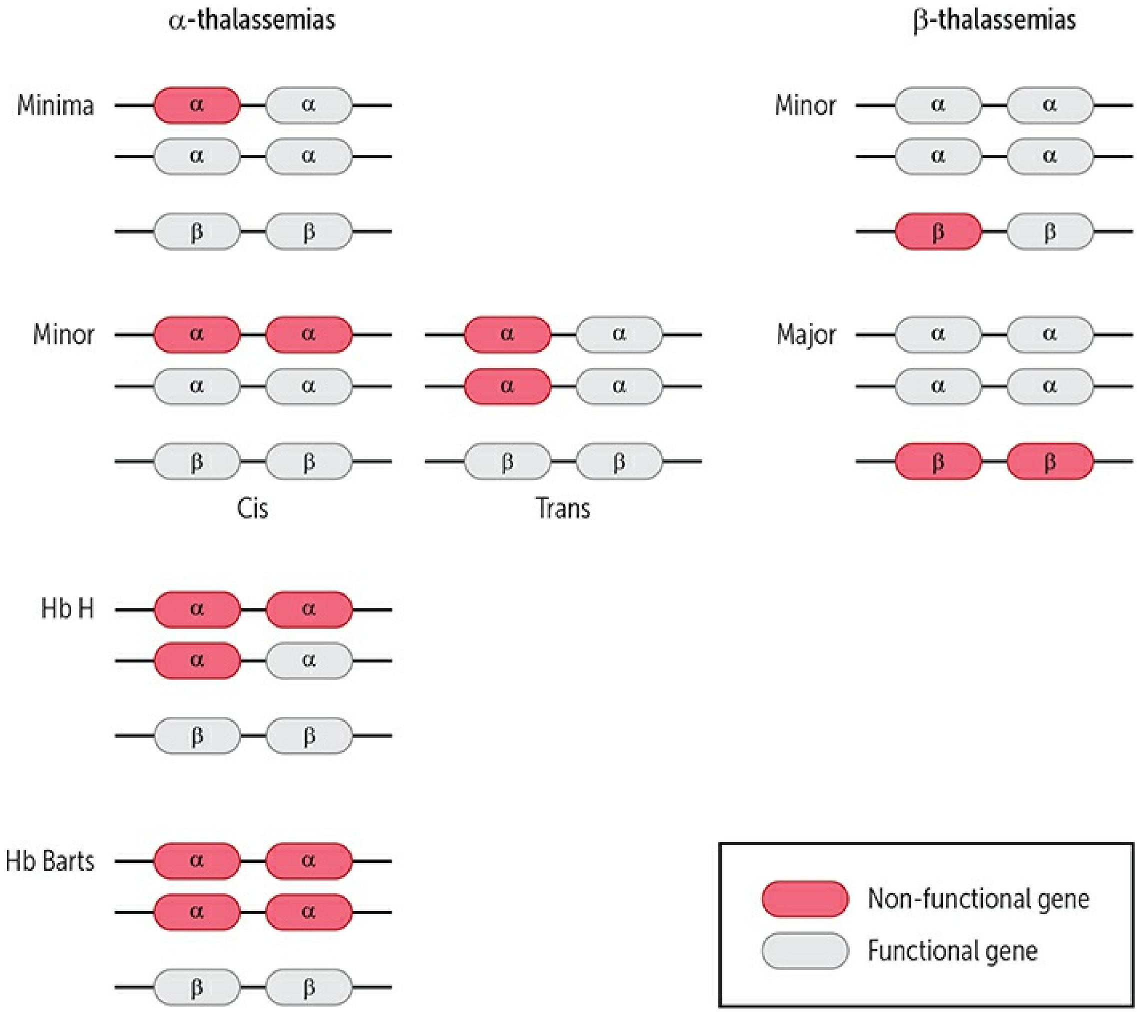

α-thalassemias
β-thalassemias
Minima
Minor
Cis
Trans
Hb H
Hb Barts
Minor
Major
α
β
Non-functional gene
Functional gene

FIGURE 2.7-10. **Gene function in α- and β-thalassemia.** (Reproduced with permission from USMLE-Rx.com.)

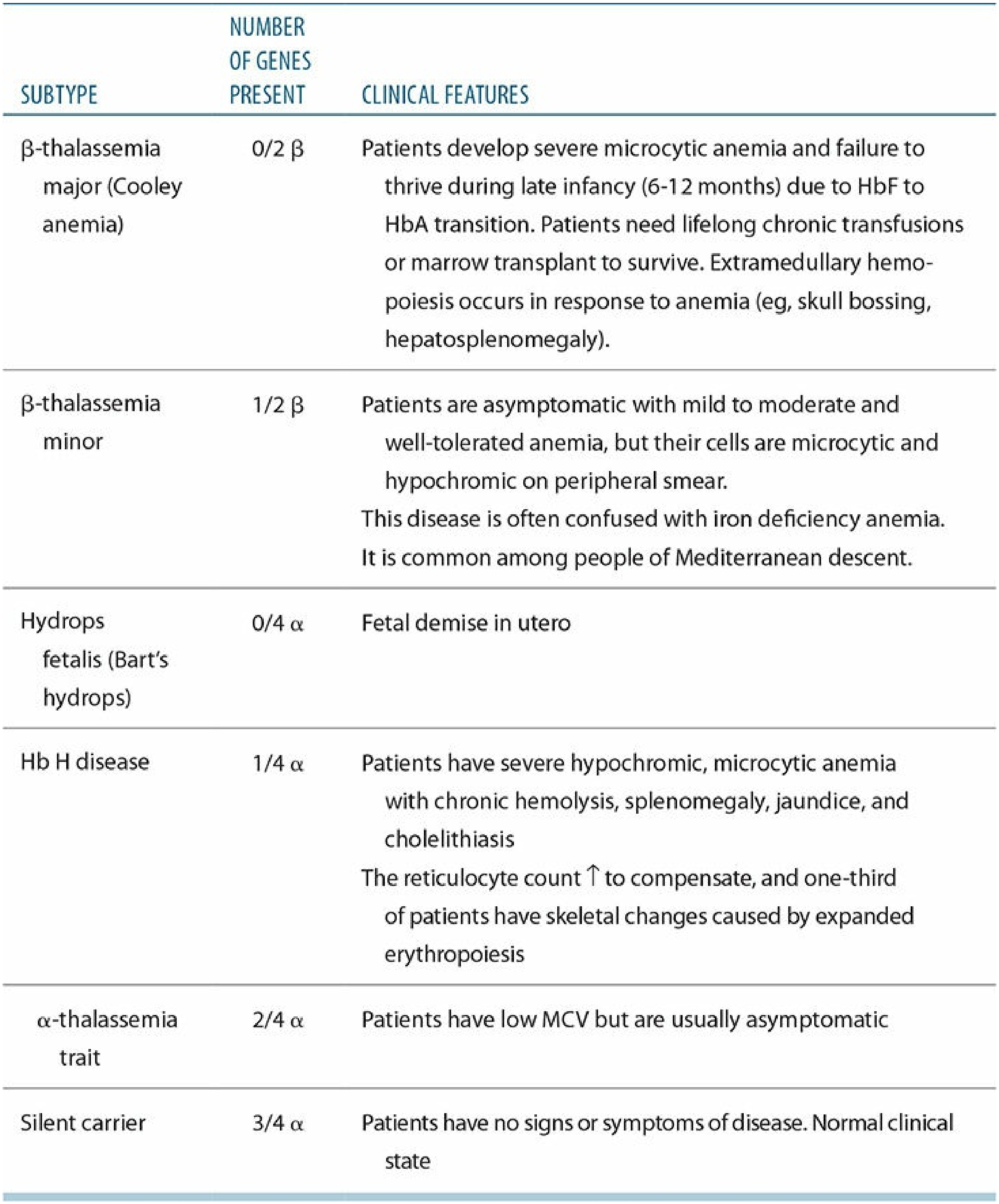
Thalassemias

Hereditary disorders involving ↓ or absent production of normal globin chains of Hb. α-Thalassemia is caused by a gene deletion of one or more of the four genes that encode α-hemoglobin. β-Thalassemia results from a point mutation of one or both of the two genes encoding β-hemoglobin.

History/PE

Thalassemia is most common among people of African, Middle Eastern, and Asian descent. Disease presentation varies with the number of genes missing (see Table 2.7-11). A typical case can be an asymptomatic or fatigued individual with a microcytic anemia and normal iron studies.

TABLE 2.7-11. **Differential Diagnosis of Thalassemias**



SUBTYPE	NUMBER OF GENES PRESENT	CLINICAL FEATURES
β-thalassemia major (Cooley anemia)	0/2 β	Patients develop severe microcytic anemia and failure to thrive during late infancy (6-12 months) due to HbF to HbA transition. Patients need lifelong chronic transfusions or marrow transplant to survive. Extramedullary hemopoiesis occurs in response to anemia (eg, skull bossing, hepatosplenomegaly).
β-thalassemia minor	1/2 β	Patients are asymptomatic with mild to moderate and well-tolerated anemia, but their cells are microcytic and hypochromic on peripheral smear. This disease is often confused with iron deficiency anemia. It is common among people of Mediterranean descent.
Hydrops fetalis (Bart's hydrops)	0/4 α	Fetal demise in utero
Hb H disease	1/4 α	Patients have severe hypochromic, microcytic anemia with chronic hemolysis, splenomegaly, jaundice, and cholelithiasis The reticulocyte count ↑ to compensate, and one-third of patients have skeletal changes caused by expanded erythropoiesis
α-thalassemia trait	2/4 α	Patients have low MCV but are usually asymptomatic
Silent carrier	3/4 α	Patients have no signs or symptoms of disease. Normal clinical state

Diagnosis

Most accurate test is Hb electrophoresis (normal in α trait, α silent carrier). For α-thalassemia, genetic studies are the most accurate tests. All forms of thalassemia have a normal red cell distribution width (RDW). Only three-gene deletion α-thalassemia is associated with Hb H and ↑ reticulocyte count.

Treatment

- Most patients do not require treatment (trait is not treated).
- Those with β-thalassemia major and Hb H disease are often transfusion dependent (chronic, lifelong transfusion) and require oral iron chelators (deferasirox or deferiprone)

or a parenteral iron chelator (deferoxamine) to prevent overload.

KEY FACT

Mentzer index: MCV divided by RBC count (MCV/RBC). Can help distinguish between thalassemia and iron deficiency anemia. Mentzer index <13 suggests thalassemia and >13 suggests iron deficiency anemia.

KEY FACT

Patients with Fanconi anemia can be identified on physical examination by café au lait spots, short stature, and radial/thumb hypoplasia/aplasia.

NONHEMOLYTIC, NORMOCYTIC ANEMIAS

Aplastic Anemia

Failure of blood cell production (pancytopenia) caused by destruction of bone marrow cells. It may be hereditary, as in Fanconi anemia (genetic analysis will show chromosomal breaks); may have an autoimmune or viral etiology (HIV, parvovirus B19, Epstein-Barr virus [EBV], cytomegalovirus [CMV], hepatitis); or may result from exposure to toxins (cleaning solvents, insecticides, benzene), radiation, or drugs (sulfa, chloramphenicol, propylthiouracil, carbamazepine, alcohol, methimazole, chemotherapy).

Q

A 30-year-old man from Greece comes to the physician’s office, complaining of chronic fatigue. He has no significant past medical history and is on no medications. A CBC shows Hb of 10.4 and MCV of 71. The physician starts him on oral iron supplements and sees him back in 4 weeks with no change in the CBC. What is the most likely diagnosis?

History/PE

Patients are pancytopenic, with symptoms resulting from a lack of RBCs, WBCs, and platelets: pallor, fatigue, weakness, a tendency to infection, petechiae, bruising, and bleeding.

Diagnosis

- Diagnosed by clinical presentation and CBC
- **Most accurate test:** Bone marrow biopsy revealing hypocellularity and space occupied by fat

Treatment

- **Supportive therapy:** Blood transfusion for anemia, antibiotics for infection, platelets for bleeding
- Consideration of allogenic bone marrow transplantation (BMT) in young patients with a matched donor. Some severe cases—patients without a stem cell donor or patients not suitable for BMT (>50 years of age)—call for immunosuppression with cyclosporine, antithymocyte globulin (ATG), and eltrombopag to prevent autoimmune marrow destruction. Tacrolimus is an alternative to cyclosporine. Infections should be treated

aggressively.

KEY FACT

Diamond-Blackfan syndrome presents with pure red cell aplasia and congenital anomalies, such as triphalangeal thumbs and cleft lip.

HEMOLYTIC, NORMOCYTIC ANEMIAS

Occurs when bone marrow production is unable to compensate for ↑ destruction of circulating blood cells. Etiologies can be due to extrinsic and intrinsic hemolytic anemias as follows:

- **Extrinsic hemolytic anemias:** Autoimmune hemolytic anemia (AIHA), microangiopathic hemolytic anemia (TTP, HUS, DIC), macroangiopathic hemolytic anemia (prosthetic heart valves, aortic stenosis), hemolytic anemia due to infection (eg, malaria, *Babesia*)
- **Intrinsic hemolytic anemias:** Glucose 6-phosphate dehydrogenase (G6PD) deficiency, paroxysmal nocturnal hemoglobinuria (PNH), hereditary spherocytosis (see Fig. 2.7-11), sickle cell anemia.

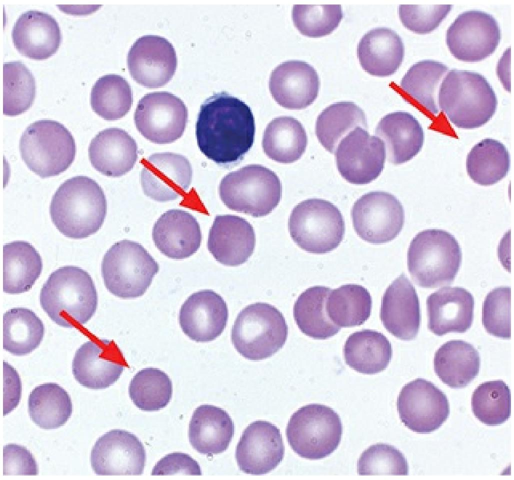


FIGURE 2.7-11. **Spherocytes.** These RBCs *(arrows)* lack areas of central pallor. Spherocytes are seen in autoimmune hemolysis and in hereditary spherocytosis. (Reproduced with permission from Bun HF, Aster JC. *Pathophysiology of Blood Disorders.* New York, NY: McGraw Hill; 2011.)

History/PE

- Present with pallor, fatigue, tachycardia, and tachypnea.
- Jaundice often present too. Hepatosplenomegaly, pigmented gallstones (pigment caused by ↑ indirect bilirubin), and leg ulcers (poor blood flow) may be noted.

MNEMONIC

Causes of hemolytic anemia—

MOM PASS me the GLUCOSE

Microangiopathic hemolytic anemia (TTP, HUS, DIC)

Other: malaria, hypersplenism
Mechanical hemolysis
Paroxysmal nocturnal hemoglobinuria
Autoimmune anemia
Sickle cell disease
Spherocytosis
GLUCOSE 6-phosphate dehydrogenase deficiency

A

The most likely diagnosis is β-thalassemia minor. The physician should recognize that this patient has a microcytic anemia that did not respond to iron supplements (probably has normal iron studies) and is from the Mediterranean.

Diagnosis

- **Lab tests:** CBC, reticulocytes, electrolytes, liver function tests (LFTs), haptoglobin, urinary urobilinogen
- ↓ Hct, ↑ LDH, ↑ Hct bilirubin, ↑ reticulocyte count, ↓ haptoglobin are commonly seen. Folate deficiency (folate is used from increased cell production) and hyperkalemia (↑ cell breakdown) may be seen. Urine is dark with hemoglobinuria, and there is ↑ excretion of urinary and fecal urobilinogen. A slight ↑ MCV (macrocytosis) is caused by large reticulocytes.
- **Blood films:** Hypochromic microcytic anemia (thalassemia), sickle cells (sickle cell anemia), schistocytes (microangiopathic hemolytic anemia), abnormal cells (hematologic malignancy), spherocytes (hereditary spherocytosis or AIHA), Heinz bodies (seen with supravital staining), bite cells (G6PD deficiency).
- Direct antiglobulin (Coombs) test to identify AIHA.

Treatment

Varies with the cause of hemolytic anemia (see later) but often includes corticosteroids to address immunologic causes and iron supplementation to replace losses. Splenectomy or transfusions are helpful in severe cases.

G6PD DEFICIENCY

An X-linked recessive defect in G6PD, causing the inability to generate glutathione reductase, leaving RBCs susceptible to hemolytic anemia following oxidant stress.

- **History/PE:** Patients are often males of Mediterranean or African descent who present with sudden anemia, episodic dark urine, and jaundice and who have a normal-sized spleen with an infection or use drugs that induce oxidative damage to RBCs. Common triggers include infections (most common), fava beans, isoniazid, nitrofurantoin, dapsone, sulfa drugs (trimethoprim-sulfamethoxazole [TMP-SMX]), and antimalarials (quinines).

KEY FACT

A classic presentation of G6PD deficiency is a Black male patient presenting with fatigue, dark urine, and shortness of breath (SOB) after taking TMP-SMX for a cold.

- **Diagnosis:**
  - **Best initial test:** CBC with smear showing features of hemolysis with bite cells and Heinz bodies
  - **Most accurate test:** G6PD level 1 to 2 months after an episode (often normal during acute episode since G6PD-deficient RBCs are hemolyzed first)
- **Treatment:** There is no reversal to the hemolysis. Avoiding triggers is the mainstay of treatment.

MNEMONIC

Causes of oxidative stress in G6PD deficiency—

Sell FAVA BEANS in INDIA

Sulfa-drugs
FAVA **BEANS**
Infections (most common cause)
Nitrofurantoin
Dapsone
Isoniazid
Antimalarials (quinines)

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

CD55 (complement decay-accelerating factor) and CD59 (membrane inhibitor of reactive lysis) proteins normally found on the RBC surfaces protect them from complement-mediated hemolysis. PNH is a deficiency in glycosylphosphatidylinositol-anchor molecules that inhibit CD55/CD59 attachment or binding to RBCs, resulting in complement-mediated hemolysis and thrombosis.

- **History/PE:** PNH can manifest as iron deficiency anemia, episodic dark urine, venous thrombosis (most commonly mesenteric and hepatic vein thrombosis), pancytopenia, and abdominal pain.
- **Diagnosis:** Most accurate diagnostic test is CD55/CD59 absence via flow cytometry.
- **Treatment:** Prednisone is the best initial therapy. Allogeneic bone marrow transplant is curative. Eculizumab, a complement inhibitor, can be used for hemolysis and thrombosis. Vaccination for *Neisseria meningitidis* needs to be administered for patients receiving eculizumab.

HEREDITARY SPHEROCYTOSIS

Autosomal dominant defect or deficiency in spectrin or ankyrin, an RBC membrane protein, resulting in a loss of RBC membrane surface area and characteristic biconcave disc. RBCs are forced to take spherical shapes and are trapped and destroyed by the spleen.

- **History/PE:** Clinically presents as an extravascular hemolytic anemia with splenomegaly and jaundice. Acute cholecystitis from pigmented gallstones is a common complication.

- **Diagnosis:**
  - **Best initial test:** CBC with a normal to low MCV, ↑ MCHC, and ⊖ Coombs test. A blood smear shows spherocytes (see Fig. 2.7-10).
  - **Most accurate test:** Eosin-5 maleimide flow cytometry (replaced osmotic fragility test) and acidified glycerol lysis test.
- **Treatment:** Manage with a splenectomy (stops hemolysis, but spherocytes will remain) and chronic folic acid replacement (assists in RBC production). Patients with hereditary spherocytosis (HS) have a characteristically increased MCHC and RDW.

KEY FACT

Patients who had a splenectomy for any reason are at an increased lifelong risk for sepsis (for up to 30 years) from encapsulated bacteria and thus require pneumococcal, meningococcal, and *Haemophilus* vaccinations before the operation.

AUTOIMMUNE HEMOLYTIC ANEMIA

Autoantibodies against RBC membrane destroy blood cells, causing extravascular hemolysis.

- **Two types:**
  - **Warm:** IgG, associated with SLE, chronic lymphocytic leukemia (CLL), lymphoma, penicillin, rifampin, phenytoin, and α-methyldopa
  - **Cold:** IgM, associated with *Mycoplasma pneumonia*, EBV, and Waldenström macroglobulinemia
- **History/PE:** Presents as a hemolytic anemia
- **Diagnosis:** Direct Coombs test (see Fig. 2.7-12). AIHA is also associated with spherocytes. Cold agglutinin is the most effective test in cold AIHA.

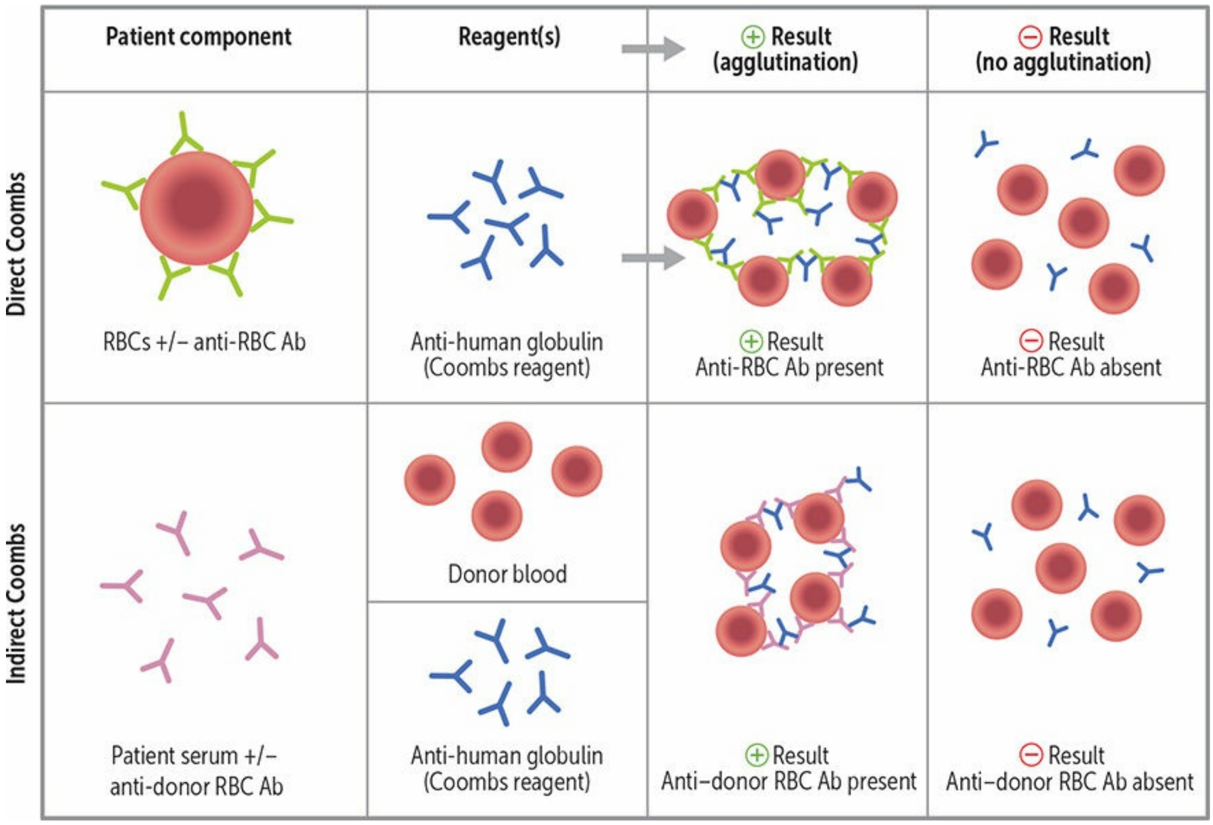

Patient component
Reagent(s)
⊕ Result (agglutination)
⊖ Result (no agglutination)
Direct Coombs
RBCs +/– anti-RBC Ab
Anti-human globulin (Coombs reagent)
⊕ Result Anti-RBC Ab present
⊖ Result Anti-RBC Ab absent
Indirect Coombs
Patient serum +/– anti-donor RBC Ab
Donor blood
Anti-human globulin (Coombs reagent)
⊕ Result Anti–donor RBC Ab present
⊖ Result Anti–donor RBC Ab absent

FIGURE 2.7-12. **Direct and indirect Coombs tests.** (Reproduced with permission from USMLE-Rx.com.)

- **Treatment:** If AIHA is mild, no treatment is necessary. Warm AIHA is treated with steroids; recurrent episodes respond to splenectomy. Severe, nonresponsive hemolysis is controlled with IVIG. Severe cold AIHA is managed by avoiding exposure to cold (keeping patient warm) ± rituximab (anti-CD20 antibody).

KEY FACT

Both AIHA and hereditary spherocytosis can present with spherocytes and positive osmotic fragility tests, but only AIHA will have a ⊕ direct Coombs's test.

MEGALOBLASTIC, MACROCYTIC ANEMIA

Impaired DNA synthesis (due to vitamin B_{12} or folate deficiency, medications) → delayed maturation of nucleus of precursor cells in bone marrow relative to maturation of cytoplasm. Vitamin B_{12} deficiency caused by pernicious anemia, malabsorption (eg, Crohn disease), pancreatic insufficiency, gastrectomy, insufficient intake (eg, veganism), *Diphyllobothrium latum* (fish tapeworm), or drugs (eg, proton pump inhibitors [PPIs], antacids, metformin). Folate deficiency caused by malnutrition (eg, chronic alcohol overuse), malabsorption, drugs (eg, methotrexate, trimethoprim, phenytoin), ↑ requirement (eg, hemolytic anemia, pregnancy). Drugs that interfere with DNA synthesis include chemotherapeutic agents (methotrexate, 6-mercaptopurine).

History/PE

- Megaloblastic anemia presents with fatigue, pallor, glossitis, cheilosis, diarrhea, loss of appetite, and headache.
- Vitamin B_{12} deficiency causes neurologic symptoms: reversible dementia and subacute combined degeneration of the spinal cord (vitamin B_{12} is required in fatty acid pathways and myelin synthesis) involving the spinocerebellar tract, lateral corticospinal tract (causing motor and upper motor neuron [UMN] signs), and dorsal column (causing sensory and lower motor neuron [LMN] signs).
- Folate deficiency does not cause neurologic symptoms. Folate supplementation in vitamin B_{12} deficiency can correct the anemia, but it worsens neurologic symptoms.

Diagnosis

- **Best initial test:** CBC (↓ Hb, ↑ MCV) with peripheral blood smear showing RBC macrocytosis and hypersegmented (six or more lobes) neutrophils (see Fig. 2.7-13). Vitamin B_{12} and folate deficiency are identical hematologically and on blood smear.

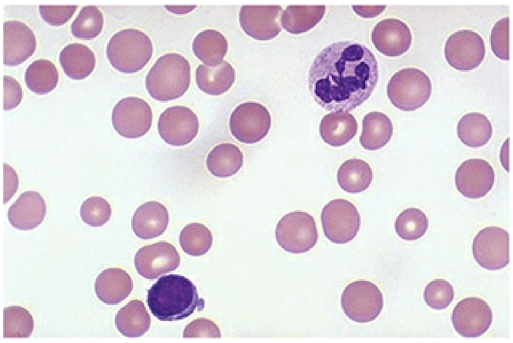


FIGURE 2.7-13. **Hypersegmentation.** The nucleus of this hypersegmented neutrophil has six lobes (six or more nuclear lobes are required). This is a characteristic finding of megaloblastic anemia. (Courtesy of Dr. Kristine Krafts.)

- ↓ reticulocyte count, pancytopenia if severe, ↑ LDH, ↑ indirect bilirubin levels.
- ↓ vitamin B_{12} and/or folate levels. If vitamin B_{12} and folate levels are nondiagnostic and clinical suspicion persists, the following adjunctive tests can be measured:
  - **Vitamin B_{12} deficiency:** ↑ methylmalonic acid (MMA) and ↑ homocysteine
  - **Folate deficiency:** Normal MMA and ↑ homocysteine
- Bone marrow sample revealing giant neutrophils and hypersegmented mature neutrophils.
- Anti-intrinsic factor and antiparietal cell antibodies in pernicious anemia.
- Schilling test, a test that determines if the cause is dietary insufficiency or malabsorption. A Schilling test measures the absorption of cobalamin via ingestion of radiolabeled cobalamin with and without intrinsic factor. This test is rarely performed.
  - **Radiolabeled vitamin B_{12} in urine:** Dietary vitamin B_{12} deficiency.
  - **No radiolabeled vitamin B_{12} in urine:** Pernicious anemia, bacterial overgrowth, or pancreatic enzyme deficiency. The hypothesis undergoes testing with the addition of intrinsic factor, antibiotics, or pancreatic enzymes to radiolabeled B_{12}.

KEY FACT

Vitamin B_{12} deficiency can be caused by infection by a tapeworm, *Diphyllobothrium latum*. Folate deficiency can occur secondary to chronic phenytoin use, causing malabsorption.

KEY FACT

Subacute combined degeneration of the spinal cord seen in vitamin B_{12} deficiency presents as pe-ripheral neuropathy, vibration and proprioception dysfunction, dementia, and spasticity.

KEY FACT

Only megaloblastic anemia (eg, due to vitamin B_{12} or folic acid deficiency) is associated with hypersegmented neutrophils (not nonmegaloblastic anemia, eg, due to chronic alcohol overuse, liver disease).

KEY FACT

Pernicious anemia increases the risk for gastric cancer and is the most common cause of vitamin B_{12} deficiency in people of European descent.

Treatment

Addressing underlying cause. Intramuscular hydroxocobalamin (if vitamin B_{12} deficiency due to malabsorption), oral vitamin B_{12} supplementation (if due to dietary causes).

PORPHYRIAS

Porphyrias are metabolic disorders caused by dysfunction in the enzymatic activity of heme synthesis, which results in the abnormal accumulation of heme precursors.

History/PE

- History reveals acute attacks.
- The physical examination can reveal signs specific to an enzymatic deficiency such as neurovisceral manifestations (abdominal pain, peripheral neuropathy) and cutaneous photosensitivity (blistering). See Table 2.7-5.

Diagnosis

- For suspected acute intermittent porphyria, measurement of porphobilinogen (PBG) in the urine at the time of the attack (sensitive and specific) can be diagnostic.
- For suspected blistering cutaneous porphyria, measurement of plasma or urine porphyrins can help confirm the diagnosis.

Treatment

- Supportive treatment (pain, nausea)
- Avoidance of triggering factors such as alcohol, smoking, OCPs
- Specific treatments in Table 2.7-12

TABLE 2.7-12. Porphyria

DISEASE	AFFECTED ENZYME	ACCUMULATED SUBSTRATE	SYMPTOMS AND TREATMENT
Acute intermittent porphyria	Porphobilinogen deaminase	Porphobilinogen, ALA	Painful abdomen, port wine–colored urine, polyneuropathy, psychiatric issues Exacerbated by factors that increase ALA synthase – drugs (CYP 450 inducers), alcohol, starvation Treated with hemin and glucose
Porphyria cutanea tarda	Uroporphyrinogen decarboxylase	Uroporphyrin causes tea-colored urine	Blistering cutaneous photosensitivity and hyperpigmentation Most common porphyria Exacerbated by alcohol consumption Causes are familial and seen in hepatitis C Treated with phlebotomy, sun avoidance, and antimalarials (hydroxychloroquine)

POLYCYTHEMIAS

Erythrocytosis (an abnormal elevation of Hct) may be either absolute (↑ RBC production) or relative (↓ plasma volume and hemoconcentration). Absolute polycythemia causes are primary (polycythemia rubra vera) or secondary (caused by hypoxia) or inappropriately ↑ EPO secretion (EPO-producing tumors).

History/PE

- Polycythemias are characterized by ↑ Hct, ↑ blood viscosity, ↓ tissue blood flow and oxygenation, and ↑ cardiac work.
- Absolute erythrocytosis is associated with hypoxia (lung disease, heavy smoking, high altitudes, obstructive sleep apnea, cyanotic congenital heart disease, or poor intrauterine environment); neoplasia (renal carcinoma, hepatocellular carcinoma); or polycythemia vera (PCV).
- A PCV is a myeloproliferative neoplasm that results from clonal proliferation of a pluripotent marrow stem cell caused by a mutation in the *JAK2*, which regulates marrow production. There is excess proliferation of RBCs, WBCs, and platelets → hyperviscosity and thrombosis, but RBCs are most significantly affected. RBCs proliferate at an exceedingly high rate despite a low level of EPO.
  - **Presentation:** Hyperviscosity syndrome. Easy bleeding/bruising from engorged blood vessels, fatigue, hypertension, thrombosis (arterial and venous), visual disturbance, neurologic deficits, headaches, dizziness, tinnitus, pruritus after a warm bath, congestive heart failure (CHF), facial plethora, and splenomegaly.
  - Commonly affects older individuals (>60 years of age).
  - Can convert to acute myeloid leukemia in a small proportion of patients.
- Relative erythrocytosis is associated with hypovolemia and dehydration: diuresis, gastroenteritis, alcohol, burns.

KEY FACT

Hemoglobinuria in a hemolytic transfusion reaction may lead to acute tubular necrosis and subsequent renal failure.

KEY FACT

Mutations in the *JAK2* gene lead to PCV and account for 30% to 50% of the cases of two other myeloproliferative disorders: Essential thrombocytopenia and myelofigrosis.

Diagnosis

- **PCV:** Best initial test is a CBC showing elevated RBCs/WBCs/platelets (↑ reticulocyte, ↑ Hb, ↑ Hct, ↑ packed cell volume) with an arterial blood gas (ABG) and EPO level. ↓ EPO, normal O_2, and Hct >60% (key finding) suggest packed cell volume. Most accurate test is the *JAK2* mutation (present in 95% of patients).
- Relative erythrocytosis also has an ↑ Hct and splenomegaly, but EPO is normal or increased, and O_2 is often low compared to packed cell volume.

KEY FACT

PCV has low EPO and normal O_2 levels. Relative erythrocytosis has normal or increased EPO with low O_2 levels.

KEY FACT

Myelodysplastic syndromes consist of stem cell disorders due to ineffective hematopoiesis → ↑ number of blasts in the bone marrow: <20% blasts comparted to AML with >20% blasts. Myelodysplastic syndromes stem from de novo mutations or from exposures (chemotherapy, radiation).

Treatment

- **PCV:** Target is hematocrit <45%. Phlebotomy and aspirin provide symptom relief and prevent thrombosis. Hydroxyurea reduces cell counts. Elevated uric acid levels are common due to increased cell turnover. This can lead to gout and kidney stones. Hydroxyurea-resistant disease is treated with ruxolitinib (JAK inhibitor).
- **Relative erythrocytosis:** Treatment should address the underlying cause and treat symptoms with phlebotomy.

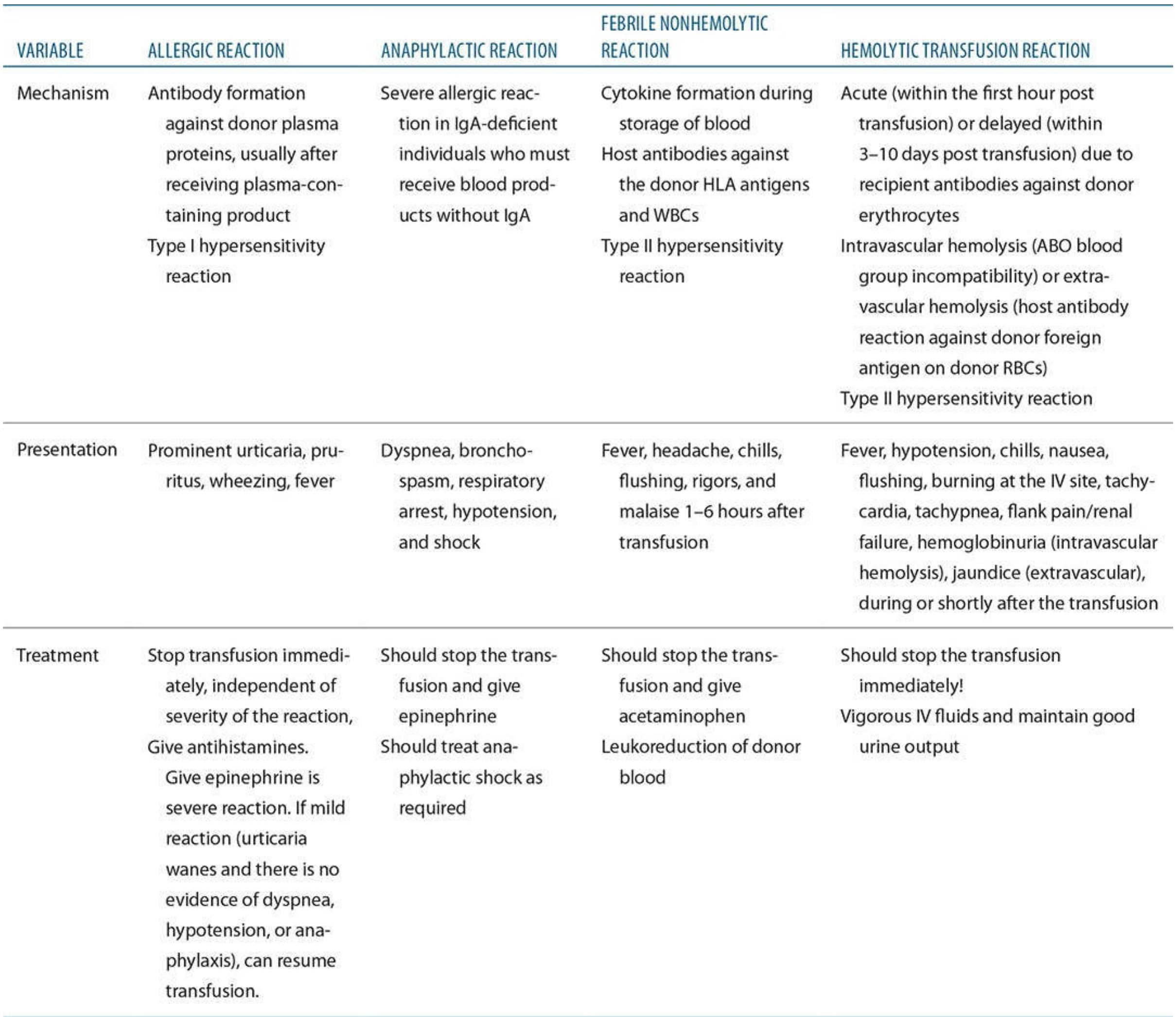
Q

A 49-year-old man comes into the clinic complaining of “tiredness” over the last several months. His past medical history is significant for hypertension, diabetes mellitus, and alcohol overuse. A CBC reveals a low Hb and an MCV of 115 Fl. What is the most likely cause of his anemia?

BLOOD TRANSFUSION REACTIONS

Transfusions are generally safe but may result in adverse reactions (see Table 2.7-13). Febrile nonhemolytic and allergic reactions are the most common, occurring in 3% to 4% of all transfusions.

TABLE 2.7-13. **Transfusion Reactions**



VARIABLE	ALLERGIC REACTION	ANAPHYLACTIC REACTION	FEBRILE NONHEMOLYTIC REACTION	HEMOLYTIC TRANSFUSION REACTION
Mechanism	Antibody formation against donor plasma proteins, usually after receiving plasma-containing product Type I hypersensitivity reaction	Severe allergic reaction in IgA-deficient individuals who must receive blood products without IgA	Cytokine formation during storage of blood Host antibodies against the donor HLA antigens and WBCs Type II hypersensitivity reaction	Acute (within the first hour post transfusion) or delayed (within 3–10 days post transfusion) due to recipient antibodies against donor erythrocytes Intravascular hemolysis (ABO blood group incompatibility) or extravascular hemolysis (host antibody reaction against donor foreign antigen on donor RBCs) Type II hypersensitivity reaction
Presentation	Prominent urticaria, pruritus, wheezing, fever	Dyspnea, bronchospasm, respiratory arrest, hypotension, and shock	Fever, headache, chills, flushing, rigors, and malaise 1–6 hours after transfusion	Fever, hypotension, chills, nausea, flushing, burning at the IV site, tachycardia, tachypnea, flank pain/renal failure, hemoglobinuria (intravascular hemolysis), jaundice (extravascular), during or shortly after the transfusion
Treatment	Stop transfusion immediately, independent of severity of the reaction, Give antihistamines. Give epinephrine is severe reaction. If mild reaction (urticaria wanes and there is no evidence of dyspnea, hypotension, or anaphylaxis), can resume transfusion.	Should stop the transfusion and give epinephrine Should treat anaphylactic shock as required	Should stop the transfusion and give acetaminophen Leukoreduction of donor blood	Should stop the transfusion immediately! Vigorous IV fluids and maintain good urine output

KEY FACT

Premedication with acetaminophen and diphenhydramine is sometimes used to prevent minor transfusion reactions.

A

The patient has megaloblastic anemia caused by either a vitamin B_{12} or folate deficiency. His history of alcohol dependence strongly suggests folate deficiency, as that is the most common cause of megaloblastic anemia in people with a history of acute/chronic alcohol overuse.

WHITE BLOOD CELL DISORDERS

NEUTROPENIA

An absolute neutrophil count (ANC) <1500 cells/mm^3, where ANC = (WBC count) × (%

bands + % segmented neutrophils). Neutropenia may be caused by a combination of ↓ production, migration away from the vascular space, and ↑ destruction or utilization. It may be acquired or intrinsic. The most common causes of neutropenia in adults are infections and drugs. Other common causes include diseases that infiltrate the bone marrow such as leukemias or lymphomas, aplastic anemias, or vitamin B_{12}/folate deficiencies.

Felty syndrome: Neutropenia along with splenomegaly and rheumatoid arthritis

History/PE

- Patients are at ↑ risk for infection. Severe infections are typical when <500 cells/mm^3.
- Acute neutropenia: Associated with *Staphylococcus aureus, Pseudomonas, E coli, Proteus*, and *Klebsiella sepsis.*
- Chronic and autoimmune neutropenia: Presents with recurrent sinusitis, stomatitis, gingivitis, and perirectal infections rather than sepsis. Some chronic neutropenias are accompanied by splenomegaly (Felty syndrome, Gaucher disease, sarcoidosis).
- The physician should look for drug or toxin exposure, infection, autoimmunity, or neoplastic disease.

Diagnosis

- **Best initial test:** CBC with a peripheral blood smear. Neutropenia is followed up with ANC and thrombocytopenia or anemia with bone marrow aspiration and biopsy.
- Serum immunologic evaluation, antinuclear antibody (ANA) levels, and a workup for collagen vascular disease may be merited.

Treatment

- **Infection management:** Neutropenic patients cannot mount an effective inflammatory response.
- It is important to discontinue drugs implicated in neutropenia.
  - Neutropenic fever: In the context of neutropenia, fever is a medical emergency that calls for immediate treatment with broad-spectrum antibiotics such as cefepime that provide *Pseudomonas* coverage. Suspected fungal infections also call for appropriate treatment.
  - Hematopoietic stem cell factors such as granulocyte colony stimulating factor (G-CSF) (filgrastim) can be used to shorten the duration of neutropenia. Rarely, IVIG and allogeneic BMT may be used.

Neutropenic Fever

Defined as a single oral temperature of ≥38.3°C (≥101°F) in a neutropenic patient or a temperature of ≥38°C (≥100.4°F) for ≥1 hour in a neutropenic patient (ie, an ANC <500 cells/mm^3).

KEY FACT

The ANC (cells/mm^3) can be obtained by multiplying the total WBCs found on CBC by percentage of polymorphonuclear cells.

History/PE

Common in cancer patients undergoing chemotherapy (neutropenic nadir 7–10 days postchemotherapy). Signs of infection may be minimal or absent. Thorough physical examination but no rectal examination in light of the bleeding and infection risk.

Diagnosis

- CBC with differential, serum creatinine, blood urea nitrogen (BUN), and transaminases. Testing of blood, urine, lesion, sputum, and stool cultures. The physician should also consider testing for viruses, fungi, and mycobacteria.
- X-ray of the chest (CXR) for patients with respiratory symptoms; a CT scan to evaluate for abscesses or other occult infection.

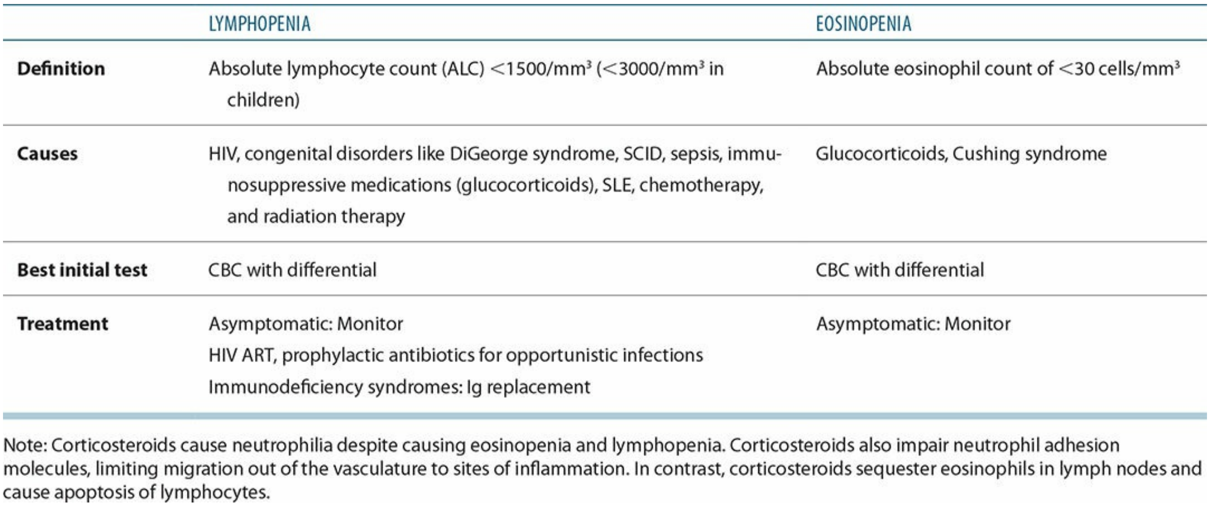
Treatment

Empiric antibiotic therapy immediately with antipseudomonal agent (cefepime, piperacillin-tazobactam) and vancomycin for methicillin-resistant *S aureus* (MRSA) coverage in patients with indwelling catheters, pneumonia, or cutaneous abscess. Routine use of colony-stimulating factors is not indicated. If fevers persist after 72 hours despite antibiotic therapy, the physician should start antifungal treatment (eg, amphotericin B or caspofungin).

LYMPHOPENIA AND EOSENOPENIA

An absolute lymphocyte count (ALC) <1500/mm^3, where ALC (cells/microL) = WBC (cells/microL) × percent lymphocytes ÷ 100. The most common causes of lymphopenia include viral infections such as HIV, congenital disorders like DiGeorge syndrome, severe combined immunodeficiency (SCID), sepsis, immunosuppressive medications (glucocorticoids), SLE, chemotherapy, and radiation therapy. Table 2.7-14 presents lymphopenia versus eosinopenia.

TABLE 2.7-14. **Lymphopenia vs Eosinopenia**



	LYMPHOPENIA	EOSINOPENIA
Definition	Absolute lymphocyte count (ALC) <1500/mm^3 (<3000/mm^3 in children)	Absolute eosinophil count of <30 cells/mm^3
Causes	HIV, congenital disorders like DiGeorge syndrome, SCID, sepsis, immunosuppressive medications (glucocorticoids), SLE, chemotherapy, and radiation therapy	Glucocorticoids, Cushing syndrome
Best initial test	CBC with differential	CBC with differential
Treatment	Asymptomatic: Monitor HIV ART, prophylactic antibiotics for opportunistic infections Immunodeficiency syndromes: Ig replacement	Asymptomatic: Monitor

Note: Corticosteroids cause neutrophilia despite causing eosinopenia and lymphopenia. Corticosteroids also impair neutrophil adhesion molecules, limiting migration out of the vasculature to sites of inflammation. In contrast, corticosteroids sequester eosinophils in lymph nodes and cause apoptosis of lymphocytes.

History/PE

Patients are at ↑ risk for recurrent infections (especially opportunistic bacterial and fungal infections in HIV) and autoimmune disorders.

Diagnosis

Best initial test: CBC with a peripheral blood smear. Neutropenia is followed up with ANC and thrombocytopenia or anemia with bone marrow aspiration and biopsy.

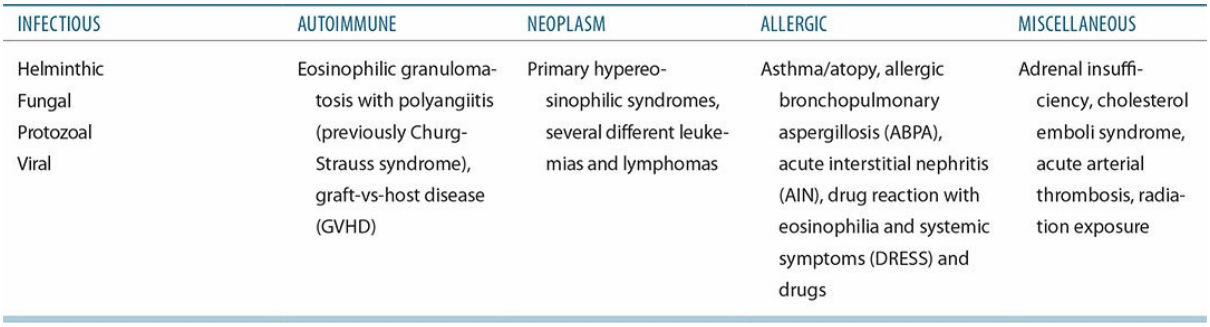
Treatment

- Asymptomatic lymphopenia is usually not treated, but is monitored.
- HIV is treated with antiretroviral therapy. Prophylactic antibiotics for opportunistic infections in HIV are the standard of care.
- In case of immunodeficiency syndromes, immunoglobulin replacement may be considered.

EOSINOPHILIA

An absolute eosinophil count ≥500/mm^3. Eosinophilia as a primary disorder is rare. The most common cause in the developed world is allergy, whereas in the developing world, it is parasitic infection. Table 2.7-15 summarizes the different etiologies of hypereosinophilia.

TABLE 2.7-15. Etiologies of Hypereosinophilia



INFECTIOUS	AUTOIMMUNE	NEOPLASM	ALLERGIC	MISCELLANEOUS
Helminthic Fungal Protozoal Viral	Eosinophilic granulomatosis with polyangiitis (previously Churg-Strauss syndrome), graft-vs-host disease (GVHD)	Primary hypereosinophilic syndromes, several different leukemias and lymphomas	Asthma/atopy, allergic bronchopulmonary aspergillosis (ABPA), acute interstitial nephritis (AIN), drug reaction with eosinophilia and systemic symptoms (DRESS) and drugs	Adrenal insufficiency, cholesterol emboli syndrome, acute arterial thrombosis, radiation exposure

MNEMONIC

Causes of secondary eosinophilia—

NAAACPDD

Neoplasm
Allergies
Asthma
Atopy
Collagen vascular disease
Parasites (eg *Trichinella* or *Toxocara*)
Drug

Common Presentations of Eosinophilia

Allergic bronchopulmonary aspergillosis (ABPA): Allergic reaction in the lungs due to *Aspergillus fumigatus*. Commonly observed in patients with asthma and cystic fibrosis. The chronic inflammation and mucoid impaction can result in lung damage, particularly bronchiectasis and fibrosis.

Eosinophilic granulomatosis with polyangiitis (EGPA): A type of vasculitis also known as Churg-Strauss syndrome, which consists of chronic rhinosinusitis, asthma, and prominent peripheral blood eosinophilia

Chronic eosinophilic pneumonia (CEP): Idiopathic disorder caused by high accumulation of eosinophils in the interstitium of the lungs

History/PE

- Procurement of travel, medication, and diet history.
- Inquiry into predisposing conditions, including atopy, asthma, sinus symptoms, cystic fibrosis, peripheral neuropathy, and lymphoma/leukemia.
- Examination directed toward cause. Patients with hypereosinophilic syndrome (HES) may present with fever, anemia, and prominent cardiac findings (emboli from mural thrombi, abnormal ECGs, congestive heart failure [CHF], murmurs).
- Eosinophils able to infiltrate and affect other organs as well (cutaneous, respiratory, GI, and nervous systems).
- The absolute eosinophil count does not accurately predict organ damage.

Diagnosis

- CBC with differential. Cerebrospinal fluid (CSF) analysis showing eosinophilia is suggestive of a drug reaction or infection with coccidioidomycosis or a helminth.
- Hematuria with eosinophilia is a possible sign of schistosomiasis.
- **ABPA:** Serum IgE against *A fumigatus* or elevated total serum IgE concentration.
- **EGPA:** Eosinophilia (≥1500 cells/microL), asthma, rhinosinusitis, and evidence on histopathology of eosinophilic infiltration with or without vasculitis.
- **CEP:** Bronchoalveolar lavage showing eosinophilia with CT chest imaging findings of opacities.

Q

A 35-year-old man is airlifted to the emergency department after a motor vehicle accident. He requires multiple transfusions, which stabilize his blood pressure (BP) and Hb. The following morning, he is transferred to his hospital room, where he begins to complain of numbness in his fingers. A prolonged QT interval is noted on an ECG. What is the most likely diagnosis?

Treatment

Immediate treatment: New-onset cardiac findings, eosinophilia >100,000/mm^3, and drug reaction with eosinophilia and systemic symptoms (DRESS) must be spotted early and should be treated with steroids and discontinuation of offending agents.

Nonemergency treatment: Several steroid-sparing agents can be considered.

- **Mepolizumab:** A monoclonal antibody directed against IL-5, a growth factor needed for the maturation of eosinophils and their activation
- **Benralizumab:** Monoclonal anti-IL-5 receptor alpha (IL-5R)
- **Hydroxyurea:** Works by suppressing eosinophilopoiesis
- **Other treatments:** Imatinib (features of myeloid disease), interferon alpha, alemtuzumab (anti-CD52 antibody), and JAK inhibitors (tofacitinib and ruxolitinib)

Treatment-specific indications:

- **ABPA:** Steroids are the mainstay of treatment. Antifungal therapy with itraconazole or voriconazole can be considered in addition to steroids during an acute exacerbation.
- **Omalizumab:** Humanized monoclonal antibody can be considered in the setting of poorly

controlled asthma. Mepolizumab and benralizumab can be considered in severe asthma and hypereosinophilia.

- **EGPA:** Steroids are the mainstay of treatment. During remission, steroid-sparing agents with azathioprine or methotrexate are considered. Mepolizumab and benralizumab can be considered.
- **CEP:** Steroids are the mainstay of treatment.

KEY FACT

A characteristic sign for AML subtype M3 (APL) is the Auer rod seen in the WBC cytoplasm (see Fig. 2.7-14), although Auer rods can be seen in other AML subtypes.

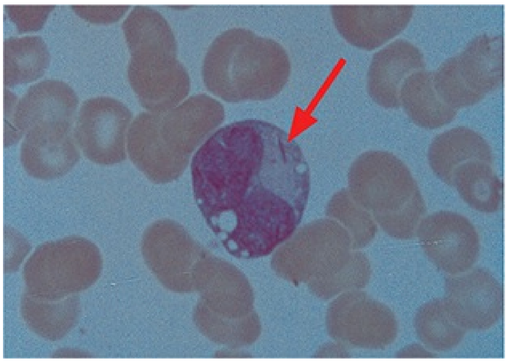


FIGURE 2.7-14. **Auer rod in AML.** The red rod-shaped structure *(arrow)* in the cytoplasm of the myeloblast is pathognomonic. (Reproduced with permission from Dr. Peter McPhedran, Yale Department of Hematology.)

LEUKEMIAS

Malignant proliferations of hematopoietic cells, categorized by the type of cell involved and their level of differentiation

Acute Leukemias

Acute myelogenous and lymphocytic leukemias are clonal disorders of early hematopoietic stem cells (blasts), resulting in unregulated growth and differentiation of WBCs in bone marrow. As the bone marrow becomes replaced by leukemia cells, patients present with features of pancytopenia: anemia (↓ RBCs), infection (↓ mature WBCs), and hemorrhage (↓ platelets).

Acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML) are two subtypes that most commonly affect children and adults, respectively.

A

This patient presents with symptoms of hypocalcemia following multiple blood transfusions. Blood products often contain citrate, which binds to serum calcium, leading to hypocalcemia, which can cause prolonged QT intervals.

History/PE

- Rapid onset and progression. Patients present with signs and symptoms of anemia (pallor, fatigue), thrombocytopenia (petechiae, purpura, bleeding), infections (ineffective and immature WBCs), and disseminated intravascular coagulation (DIC, most commonly seen in acute promyelocytic leukemia [APL]). Medullary expansion into the periosteum may lead to bone pain (common in ALL).

- Physical examination may show hepatosplenomegaly and swollen/bleeding gums from leukemic infiltration and ↓ platelets. Leukemic cells also infiltrate the skin and the central nervous system (CNS).

Diagnosis

- **Best initial test:** CBC with smear showing blast cells.
- **Most accurate test:** Bone marrow biopsy with flow cytometry to classify leukemia type.
- Marrow that is infiltrated with blast cells is consistent with leukemia. In AML, the leukemic cells are myeloblasts; in ALL, they are lymphoblasts. These cells can be distinguished by morphology (see Fig. 2.7-15), cytogenetics, and immunophenotyping (see Table 2.7-16).

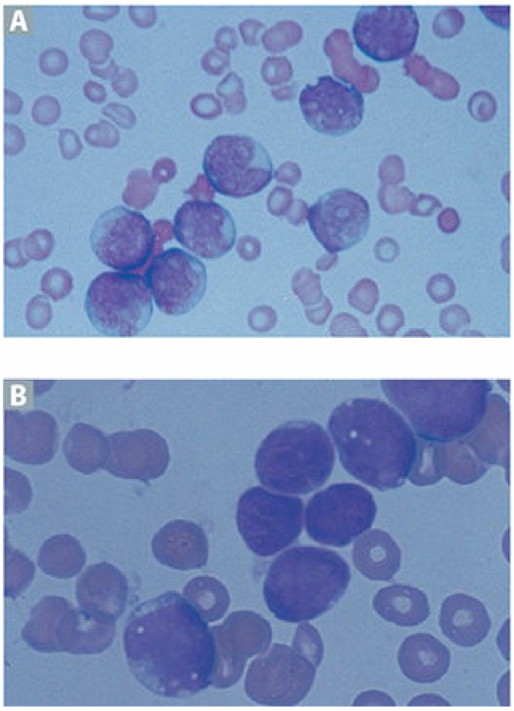


FIGURE 2.7-15. **AML and ALL on peripheral smear**. **(A)** AML. Large, uniform myeloblasts with round or kidney-shaped nuclei and prominent nucleoli are characteristic. **(B)** ALL. Peripheral blood smear reveals numerous large, uniform lymphoblasts, which are large cells with a high nuclear-to-cytoplasmic ratio. Some lymphoblasts have visible clefts in their nuclei. (Reproduced with permission from Dr. Peter McPhedran, Yale Department of Hematology.)

TABLE 2.7-16. **Myeloblasts vs Lymphoblasts**

VARIABLE	MYELOBLAST	LYMPHOBLAST
Size	Larger (2–4 times RBC)	Smaller (1.5–3.0 times RBC)
Amount of cytoplasm	More	Less
Nucleoli	Conspicuous	Inconspicuous
Granules	Common, fine	Uncommon, coarse
Auer rods	Present in 50% of cases	Absent
Myeloperoxidase	⊕	⊖
Terminal deoxynucleotidyltransferase (TdT)	⊖	⊕

- WBC count can be elevated, but the cells are dysfunctional, and patients may be neutropenic with a history of frequent infection. If the WBC count is very high (eg, >100,000/mm^3), there is a risk for leukostasis (blasts occluding the microcirculation, leading to pulmonary edema, CNS symptoms, ischemic injury, and DIC).

Treatment

- In general, ALL and AML cases are treated with chemotherapy. Bone marrow transplantation is considered in some patients, especially those with higher risk cytogenetics and those who do not respond appropriately to upfront chemotherapy.
- All-*trans*-retinoic acid (ATRA) combined with arsenic trioxide is highly effective in APL.
- To prevent tumor lysis syndrome (hyperuricemia, hyperkalemia, hypocalcemia, renal insufficiency, as blasts are destroyed by chemotherapy), patients should be well hydrated. If WBC counts are ↑, they may also be started on allopurinol or rasburicase (often used in the pediatric population) to decrease serum uric acid as renal protection. Rasburicase is contraindicated in G6PD deficiency.
- Leukostasis syndrome may be treated with hydroxyurea ± leukapheresis to ↓ WBC count.
- Indicators of poor prognosis:
  - **ALL:** Age <1 year or >10 years; an ↑ in WBC count to >50,000/mm^3; presence of the Philadelphia chromosome t(9;22) (associated with B-cell cancer); CNS involvement at diagnosis
  - **AML:** Age >60 years; elevated LDH; poor-risk or complex karyotype

Chronic Lymphocytic Leukemia

A malignant, clonal proliferation of mature but functionally incompetent lymphocytes that accumulate in the bone marrow, peripheral blood, lymph nodes, spleen, and liver. All CLL cases involve well-differentiated B lymphocytes. Primarily affects older adults (median age 65 years); the male-to-female ratio is 2:1.

History/PE

Often asymptomatic; patients present with fatigue, malaise, and infection. Common physical findings are lymphadenopathy, hepatomegaly, and splenomegaly.

Q

A 70-year-old woman with a history of hypertension and lymphoma presents with nausea, vomiting, and fever of 2 days' duration. She just completed her second cycle of high-dose chemotherapy. She has a temperature of 38.5°C (101.3°F). Her CXR is unchanged, and her WBC count is 900/mm^3 with 25% neutrophils. After urine and blood cultures have been sent, what is the next step in management?

Diagnosis

- **Best initial test:** CBC with differential and smear showing mature lymphocytosis (B cells >500/mm^3) and characteristic smudge cells (fragile leukemia cells crushed by the slide). See Figure 2.7-16.

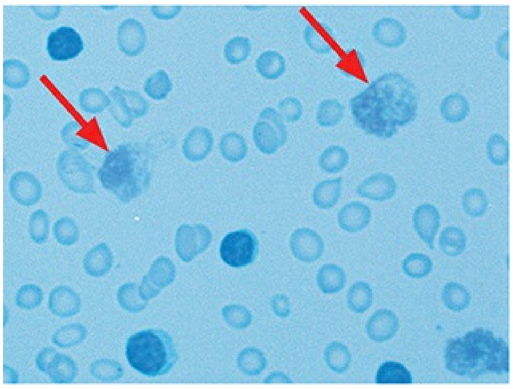


FIGURE 2.7-16. **CLL with characteristic smudge cells.** The numerous small, mature lymphocytes and smudge cells (*arrows;* fragile malignant lymphocytes are disrupted during blood smear preparation) are characteristic. (Reproduced with permission from Dr. Peter McPhedran, Yale Department of Hematology.)

- **Most accurate test:** Flow cytometry shows monoclonal B cells with CD5 and CD23 markers.
- Granulocytopenia, anemia, and thrombocytopenia are common as leukemic cells infiltrate bone marrow. Abnormal function by the leukemic cells leads to hypogammaglobulinemia.
- Bone marrow biopsy is rarely required for diagnosis but may provide prognostic information.

KEY FACT

The presence of smudge cells may indicate CLL. Smudge cells result from the coverslip crushing the fragile leukemia cells.

Treatment

- CLL often does not require treatment due to its indolent natural history. Disease progression should be monitored every 3 to 6 months.
- Initial preferred agents are ibrutinib (BTK inhibitor), rituximab (anti-CD20 mAb therapy), venetoclax (anti-BCL2 therapy)
- Treatment, however, is palliative and is often withheld until patients are symptomatic: recurrent infection, severe lymphadenopathy or splenomegaly, anemia, or thrombocytopenia (poorest prognosis).

- Although CLL has a low likelihood of long-term cure, extended disease-free intervals may be achieved with adequate treatment of symptoms. The clinical stage correlates with expected survival.

CHRONIC MYELOGENOUS LEUKEMIA

Clonal expansion of myeloid progenitor cells, leading to leukocytosis with excess granulocytes and basophils and sometimes ↑ erythrocytes and platelets as well. To truly be CML, the BCR-ABL translocation must be present. In >95% of patients, this is reflected on conventional cytogenetic analysis by the Philadelphia chromosome t(9;22). CML primarily affects middle-aged patients (median age 50 years).

A

The physician should admit the patient and begin IV antibiotics with an antipseudomonal β-lactam (eg, cefepime, piperacillin-tazobactam, meropenem, imipenem). Febrile, neutropenic patients who are on high-dose chemotherapy, have a hematologic malignancy, or have been neutropenic for >14 days should be admitted for empiric IV antibiotics.

History/PE

- Many patients are asymptomatic at diagnosis. Typical signs and symptoms are those of anemia.
- Patients can have splenomegaly with left upper quadrant (LUQ) pain and early satiety. Constitutional symptoms of weight loss, anorexia, fever, and chills may also be seen.
- Patients with CML in the absense of treatment go through three disease phases:
  - **Chronic:** Without treatment, this phase typically lasts 3.5 to 5 years. Infection and bleeding complications are rare.
  - **Accelerated:** This phase embodies a transition toward blast crisis, with an ↑ in peripheral and bone marrow blast counts. It should be suspected when the differential shows an abrupt ↑ in basophils and thrombocytopenia (platelet count <100,000/mm^3).

KEY FACT

The presence of smudge cells may indicate CLL. Smudge cells result from the coverslip crushing the fragile leukemia cells.

  - **Blast crisis:** A large percentage of untreated CML patients will eventually reach this phase. It resembles acute leukemia; survival is 3 to 6 months.

KEY FACT

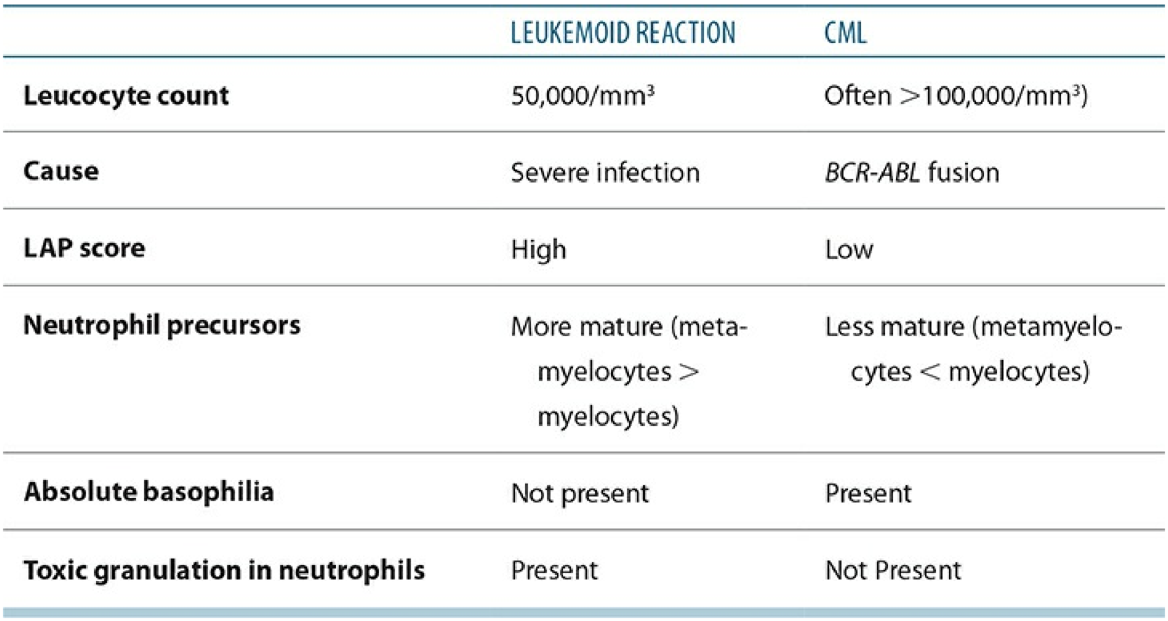
The likely diagnosis of leukemia is based on age at presentation:

- **ALL:** <13 years (but can present in any age group)
- **AML:** 13 to 40 years (but can present in any age group)
- **CML:** 40 to 60 years
- **CLL:** >60 years

Diagnosis

- **Most accurate test:** Philadelphia chromosome via polymerase chain reaction (PCR) or fluorescence in situ hybridization (FISH) analysis showing the t(9;22) translocation, although some cases lack the translocation.
- CBC often shows a very high WBC count—often >100,000/mm^3 at diagnosis, sometimes reaching >500,000/mm^3. The differential shows granulocytes (predominantly neutrophils) in all stages of maturation. Rarely, the WBC count will be so elevated as to cause a hyperviscosity syndrome.
- CML can be confused clinically with a leukemoid reaction (acute inflammatory response to infection with ↑ neutrophils and a left shift). Leukocyte alkaline phosphatase score is low in CML and other hematologic malignancies, and LAP is high in leukemoid reactions. See Table 2.7-17.

TABLE 2.7-17. **Leukemoid Reaction vs CML 19**



	LEUKEMOID REACTION	CML
Leucocyte count	50,000/mm^3	Often >100,000/mm^3)
Cause	Severe infection	*BCR-ABL* fusion
LAP score	High	Low
Neutrophil precursors	More mature (metamyelocytes > myelocytes)	Less mature (metamyelocytes < myelocytes)
Absolute basophilia	Not present	Present
Toxic granulation in neutrophils	Present	Not Present

KEY FACT

Lymphocytosis is a common lab finding of CLL (↑ B cells) vs CML, which shows granulocytosis (↑ granulocytes: neutrophils, eosinophils, or basophils).

Q 1

A 40-year-old woman sees a physician for a 6-month history of weight loss, fevers, and abdominal discomfort. Her WBC count is 56,000/mm^3. The physician orders a leukocyte alkaline phosphatase (LAP) to distinguish between a leukemoid reaction and a hematologic malignancy. What is the expected result in a leukemoid reaction?

Q 2

A 41-year-old man is diagnosed with AML. Fluorescence in situ hybridization (FISH) analysis reveals that he has APL, M3 subtype (FAB classification). What is the preferred therapy for this subtype of AML?

Treatment

- **Chronic:** Tyrosine kinase inhibitors (eg, imatinib). Young patients may be candidates for allogeneic stem cell transplantation if a matched sibling donor is available.
- **Blast crisis:** Same as that for acute leukemia, or second-generation tyrosine kinase inhibitors (eg, dasatinib, nilotinib) plus hematopoietic stem cell transplantation or a clinical trial.

Hairy Cell Leukemia

A malignant disorder of well-differentiated B lymphocytes. Hairy cell leukemia (HCL) is a rare disease that accounts for 2% of adult leukemia cases and most commonly affects older males (median age 50–55 years).

KEY FACT

Imatinib is a selective inhibitor of the BCR-ABL tyrosine kinase, the product of the t(9;22) translocation, or Philadelphia chromosome.

History/PE

- Typically presents with pancytopenia, bone marrow infiltration, and splenomegaly.
- Patients complain of weakness, fatigue, petechiae, bruising, infection (especially with atypical mycobacteria such as *Mycobacterium avium–intracellulare*), abdominal pain, early satiety, and weight loss. Presentation is similar to that of CLL except that patients rarely have lymphadenopathy.

Diagnosis

- **Best initial test:** CBC with smear showing pathognomonic “hairy cells” (mononuclear cells with many cytoplasmic projections; see Fig. 2.7-17) that stain with tartrate-resistant acid phosphatase (TRAP). Leukopenia can sometimes be seen as well.

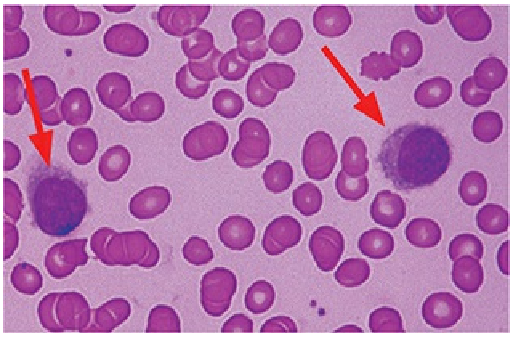


FIGURE 2.7-17. **Hairy cell leukemia.** Note the hairlike cytoplasmic projections from neoplastic lymphocytes. Villous lymphoma can also have this appearance. (Reproduced with permission from Dr. Peter McPhedran, Yale Department of Hematology.)

- **Most accurate test:** Flow cytometry identifying the “hairy cells”

Treatment

- **Best initial treatment:** Cladribine.

- **Alternative treatment options:** Pentostatin, rituximab, and interferon (IFN)-α.
- Median survival without treatment is 5 years. If left untreated, most patients will develop progressive pancytopenia and splenomegaly, eventually requiring therapy.

1 A

The LAP score would be ↑ . Hematologic malignancies, in contrast, have ↓ LAP score.

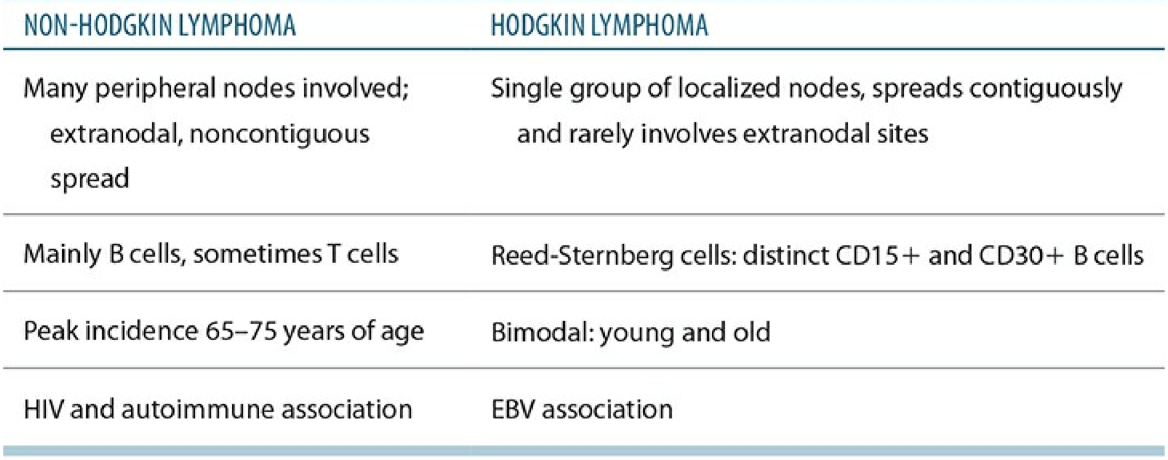
2 A

APL has a favorable prognosis, because it is responsive to ATRA therapy. This AML subtype is also associated with an ↑ incidence of DIC and a chromosomal translocation involving chromosomes 15 and 17.

LYMPHOMAS

Malignant transformations of lymphoid cells residing primarily in lymphoid tissues, especially the lymph nodes. Classically organized into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). See Table 2.7-18.

TABLE 2.7-18. Non-Hodgkin vs Hodgkin Lymphoma



NON-HODGKIN LYMPHOMA	HODGKIN LYMPHOMA
Many peripheral nodes involved; extranodal, noncontiguous spread	Single group of localized nodes, spreads contiguously and rarely involves extranodal sites
Mainly B cells, sometimes T cells	Reed-Sternberg cells: distinct CD15+ and CD30+ B cells
Peak incidence 65–75 years of age	Bimodal: young and old
HIV and autoimmune association	EBV association

Adapted with permission from Le T, et al. *First Aid for the USMLE Step 1 2018.* New York, NY: McGraw-Hill; 2018.

Non-Hodgkin Lymphoma

NHL represents a diverse group of mature B- and T-cell neoplasms. Most NHLs (almost 85%) are of B-cell origin. NHL is the most common hematopoietic neoplasm and is five times more common than HL.

History/PE

The median patient age is >50 years, but NHL may also be found in children, who tend to have more aggressive, higher-grade disease. Patient presentation varies with disease (see Table 2.7-19), but often includes painless peripheral lymphadenopathy, “B” symptoms (fevers, night sweats, weight loss), and masses on examination.

TABLE 2.7-19. **Non-Hodgkin Lymphoma Types**

TYPE	OCCURS IN	GENETICS/ETIOLOGY	COMMENTS
B-CELL NEOPLASMS			
Follicular lymphoma	Adults (mean age 55 years)	t(14;18)—translocation of heavy-chain Ig (14) and BCL-2 (18)	Indolent course or low grade Painless waxing and waning adenopathy Localized disease (15%) may be cured with radiation therapy
Diffuse large B-cell lymphoma	Usually middle-aged and elderly	Mutations in BCL-2, BCL-6, and MYC	Intermediate grade Most common NHL in adults Often presents with single rapidly growing mass High cure rate with R-CHOP therapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
Burkitt lymphoma	Children and adolescents	t(8;14)—translocation of c-myc (8) and heavy-chain Ig (14)	High grade, "starry sky" appearance on lesion biopsy Jaw lesion in Africa, abdominal lesion in Americas Associated with EBV and t(8;14) translocation Aggressive treatment with chemotherapy
Mantle cell lymphoma	Older adult Males	t(11;14)—translocation of cyclin D1 (11) and heavy-chain Ig (14), CD5+	CD5+ Rarest form of NHL
Primary CNS lymphoma	Adults	EBV related; associated with HIV/AIDS	An AIDS-defining illness Variable presentation: confusion, memory loss, seizures CNS mass (often single, ring-enhancing lesion on MRI) in immunocompromised patients Distinguished from toxoplasmosis via CSF analysis or other lab tests
T-CELL NEOPLASMS			
Adult T-cell lymphoma	Adults	Caused by HTLV (associated with IV drug use)	High grade, can progress to ALL Presents with cutaneous lesions Caused by HTLV, associated with IVDA
Mycosis fungoides/Sézary syndrome	Adults		Mycosis fungoides is a T-cell lymphoma of the skin Cutaneous eczema-like lesions and pruritus are common presentations On skin biopsy see lymphoid cells with "cerebriform" nuclei Can progress to Sézary syndrome (T-cell leukemia) with characteristic Sézary cells seen on blood smear

Adapted with permission from Le T et al. *First Aid for the USMLE Step 1 2022.* New York, NY: McGraw-Hill; 2022.

Diagnosis

- **Best initial test:** Excisional lymph node biopsy
- A CSF exam should be done in patients with HIV, neurologic symptoms, or primary CNS lymphoma.

Treatment

- Radiation and/or chemotherapy can be used as a therapy.
- Low-grade indolent NHL treatment is generally palliative.
- High-grade aggressive NHL treatment is aggressive chemotherapy with a curative approach. A common regimen is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).

KEY FACT

The treatment of high-grade NHL may be complicated by tumor lysis syndrome, in which rapid cell death releases intracellular contents and leads to hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia.

Hodgkin Lymphoma

A predominantly B-cell malignancy associated with EBV. HL has a bimodal age distribution: 30 years of age (primarily the nodular sclerosing type) and 60 years of age (mainly the lymphocyte-depleted type). It has a male predominance in childhood.

History/PE

- HL commonly presents above the diaphragm (classically as cervical adenopathy; see Fig. 2.7-18A). Infradiaphragmatic involvement suggests disseminated disease.

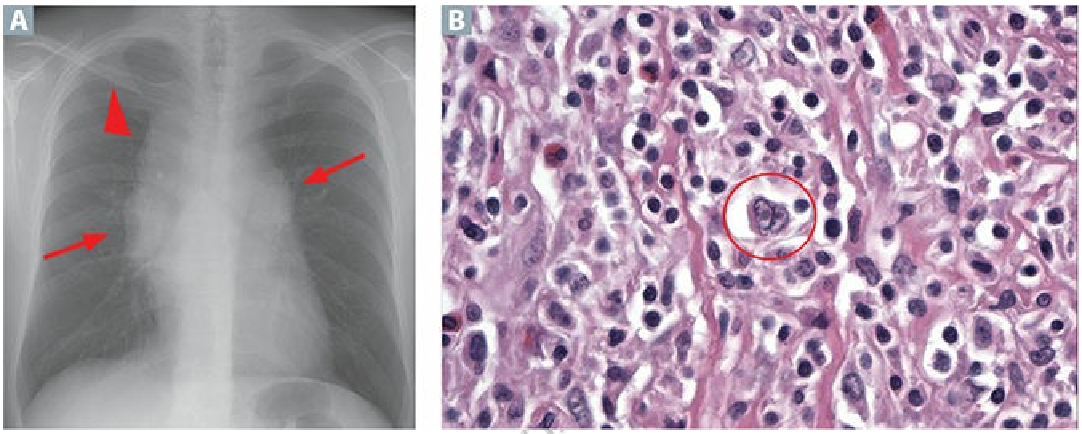


FIGURE 2.7-18. **Hodgkin lymphoma. (A)** CXR of a 27-year-old man presenting with several weeks of fevers and night sweats shows bulky bilateral hilar *(arrows)* and right paratracheal lymphadenopathy *(arrowhead)*. **(B)** Lymph node sampling shows a mixed inflammatory infiltrate and a classic binucleate Reed-Sternberg cell *(circle)* consistent with Hodgkin lymphoma. (Image A adapted with permission from Harrison NK. Cough, sarcoidosis and idiopathic pulmonary fibrosis: raw nerves and bad vibrations. Cough. 2013;9(1):9. Published 2013 Mar 6. doi:10.1186/1745-9974-9-9. Image B courtesy of Dr. Andrea Subhawong.)

- Patients can have systemic B symptoms, pruritus, and hepatosplenomegaly. Pel-Ebstein fevers (1–2 weeks of high fever alternating with 1–2 afebrile weeks) and alcohol-induced pain at nodal sites are rare signs specific for HL.

KEY FACT

On physical examination, lymph nodes suspicious for malignancy are generally described as firm, fixed, nontender, circumscribed, rubbery, and >1 cm in diameter. Benign nodes (usually from infection) are generally described as bilateral, <1 cm, mobile, and nontender (viral) or tender (bacterial).

Diagnosis

- **Best initial step:** Excisional lymph node biopsy shows the classic Reed-Sternberg cells (giant abnormal B cells with bilobar nuclei and huge, eosinophilic nucleoli, which create an “owl’s-eye” appearance; see Fig. 2.7-18B).
- Staging is based on the number of lymph node groups involved, the presence of B

symptoms, and whether the disease involves lymph nodes (both sides of the diaphragm) and extranodal sites (eg, bone marrow).

KEY FACT

Chemotherapy and radiation can lead to secondary neoplasms such as AML, NHL, breast cancer, and thyroid cancer. Preventive measures such as mammography are warranted.

Treatment

- Treatment is stage dependent, involving chemotherapy and/or radiation (in early stage disease). A common chemotherapy regimen is Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine (ABVD).
- Radiation increases the risk for premature coronary artery disease, solid tumors (eg, breast, lung, thyroid), and hypothyroidism.
- Five-year survival rates are 90% for stage I and II disease (nodal disease limited to one side of the diaphragm), 84% for stage III, and 65% for stage IV. Lymphocyte-predominant HL has the best prognosis.

PLASMA CELL DISORDERS

MULTIPLE MYELOMA

Clonal proliferation of malignant plasma cells with excessive production of monoclonal immunoglobulins (typically ineffective IgA or IgG) and/or immunoglobulin fragments (kappa/lambda light chains). Multiple myeloma (MM) primarily affects older adults, peaking in the seventh decade. Risk factors include radiation exposure and monoclonal gammopathy of undetermined significance (MGUS).

KEY FACT

Chemotherapy often induces nausea in cancer patients and should be managed with ondansetron, a serotonin 5-hydroxytryptamine (5-HT3) receptor antagonist.

MNEMONIC

Clinical features of multiple myeloma—

CRAB

Cooselycemia
Renal involvement/**R**ecurrent infections
Anemia/**A**myloidosis
Bone lytic lesions/**B**ack pain

History/PE

- Patients present with bone pain or with a pathologic fracture (MM cells infiltrate bone marrow, where they activate osteoclasts, creating lytic lesions, weak bones, and hypercalcemia).

- Patients are prone to infection (IgG and IgA produced by myeloma cells are monoclonal, thus making them ineffective) and have elevated monoclonal (M) proteins in serum and/or urine.

KEY FACT

Similar to MM, MGUS is a monoclonal expansion of plasma cells that is asymptomatic and may eventually lead to multiple myeloma (1%-2% per year). No “CRAB” findings.

Diagnosis

- **Best initial test:** Serum protein electrophoresis showing IgG or IgA monoclonal spikes (see Fig. 2.7-19), and/or serum free light chains.

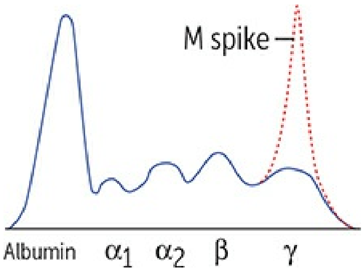


FIGURE 2.7-19. **Multiple myeloma.** Serum protein electrophoretic tracing showing M protein spike IgG/A (diagnostic of MM). Note that M protein spike IgM indicates Waldenström macroglobulinemia. (Reproduced with permission from USMLE-Rx.com.)

- **Most accurate test:** Bone marrow biopsy shows >10% monoclonal CD138+ plasma cells.
- CBC with smear may show rouleaux formation, whereas urine protein electrophoresis may show Bence Jones protein (paraprotein). Gamma gap (total serum protein – serum albumin) is often elevated.
- M protein alone is insufficient for the diagnosis of MM, as MGUS, CLL, lymphoma, Waldenström macroglobulinemia, and amyloidosis can also ↑ M protein.
- Patients should also be evaluated for anemia, hypercalcemia, and renal failure. Bone lesions are also seen with imaging such as a skeletal survey (see Fig. 2.7-20).

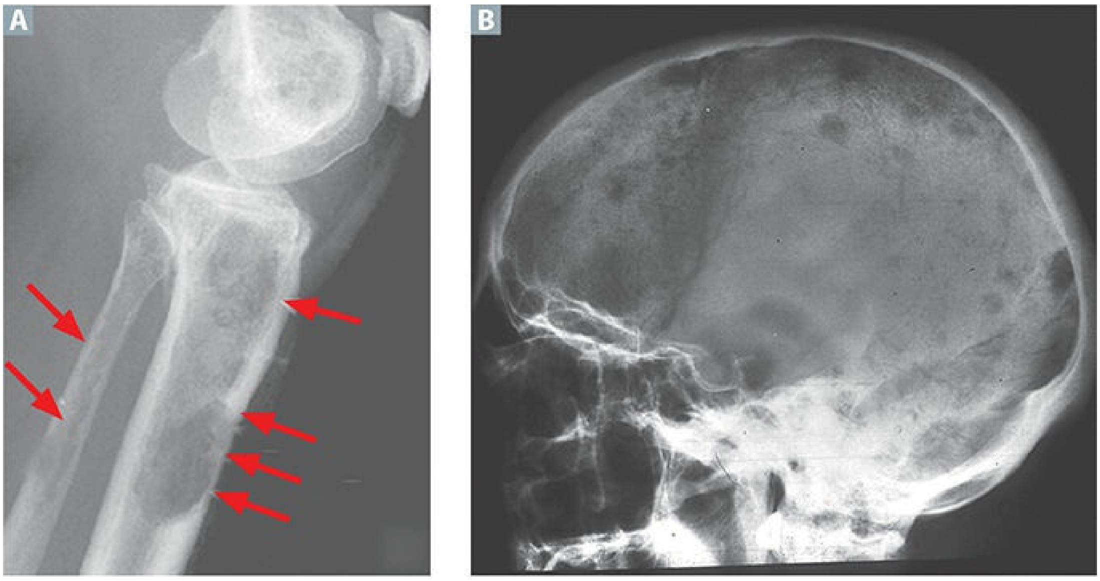


FIGURE 2.7-20. **Multiple myeloma skeletal survey.** Characteristic lytic bony lesions of multiple myeloma involving the tibia and fibula **(A)** and the skull **(B)** are seen. (Image A reproduced with permission from Lichtman MA et al. *Williams Hematology.* 8th ed. New York, NY: McGraw-Hill; 2010. Image B reproduced with permission from Kantarjian HM, Wolff RA, Koller CA. *MD Anderson Manual of Medical Oncology.* 2nd ed. New York, NY: McGraw-Hill; 2011.)

KEY FACT

MM damaging renal tubules can produce adult Fanconi syndrome.

KEY FACT

As MM is an osteoclastic process, a bone scan, which detects osteoblastic activity, may be ⊖.

Treatment

- Patients who are candidates can be treated with chemotherapy and autologous bone marrow transplant. Common chemotherapeutic agents are cyclophosphamide, bortezomib, daratumumab (anti-CD138 mAb), dexamethasone, and lenalidomide.
- Patients who are not candidates for bone marrow transplantation can be treated with daratumumab, lenalidmoide, dexamethasone, cyclophosphamide and/or bortexomib.

WALDENSTRöM MACROGLOBULINEMIA

A clonal disorder of B cells that leads to malignant monoclonal gammopathy. ↑ levels of IgM result in hyperviscosity syndrome, coagulation abnormalities, cryoglobulinemia, cold agglutinin disease (leading to AIHA), and amyloidosis. Tissue is infiltrated by IgM and neoplastic plasma cells. A chronic, indolent disease of older adults.

KEY FACT

Cryoglobulinemia and cold agglutinins are different disorders caused by IgM antibodies. Cryoglobulinemia is most often seen in hepatitis C virus (HCV) and has systemic signs such as joint pain and renal involvement. Cold agglutinins may cause finger or toe numbness and hemolytic anemia upon cold exposure and are seen with EBV, mycoplasmal infection, and Waldenström macroglobulinemia.

History/PE

- **Presents with nonspecific symptoms:** Lethargy, weight loss, and Raynaud phenomenon from cryoglobulinemia. Organomegaly and organ dysfunction can be present.
- Neurologic problems ranging from mental status changes to sensorimotor peripheral neuropathy and blurry vision (engorged blood vessels can be noted on eye exam) are also seen.
- As with MM, MGUS is a precursor to disease.

Diagnosis

- **Most accurate test:** Bone marrow biopsy and aspirate. Marrow shows abnormal plasma cells, classically with Dutcher bodies (periodic acid–Schiff [PAS]⊕ IgM deposits around the nucleus). Serum and urine protein electrophoresis and immunofixation are also used.
- Nonspecific findings include ↑ erythrocyte sedimentation rate (ESR), uric acid, LDH, and alkaline phosphatase.

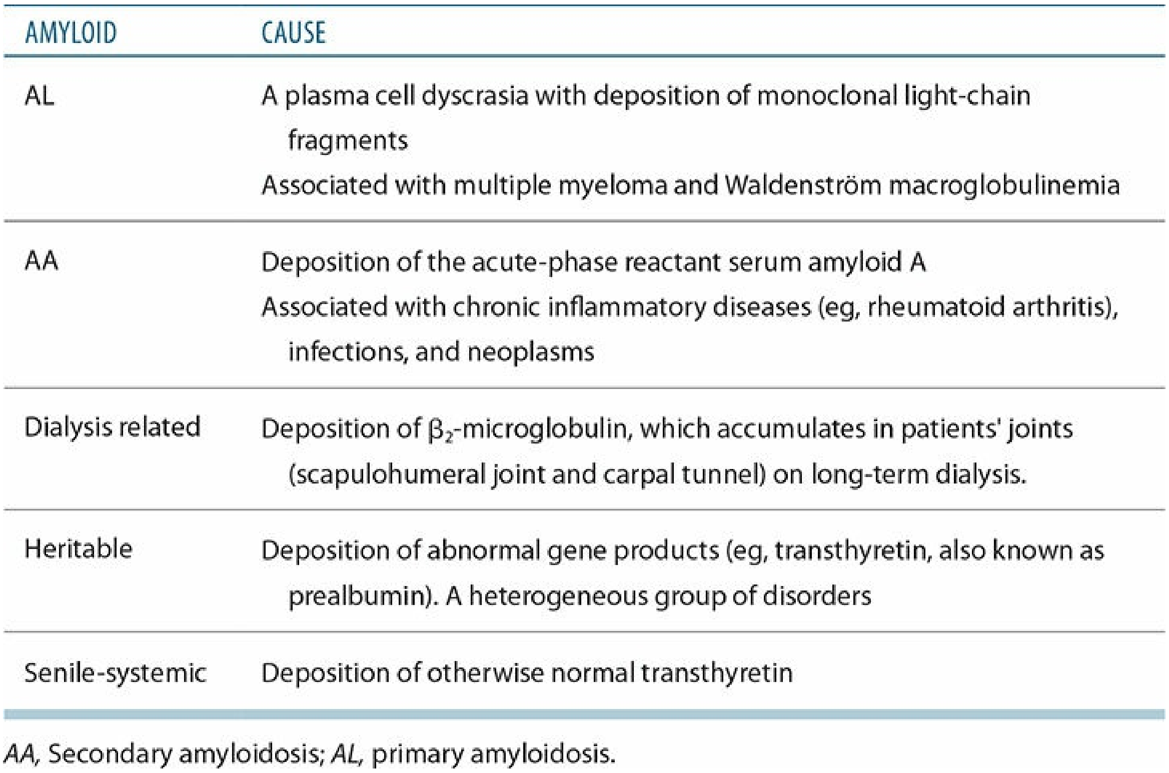
Treatment

Rituximab and chemotherapy for patients with symptomatic disease. Plasmapheresis can remove excess immunoglobulin for patients who present with signs or symptoms of hyperviscosity.

AMYLOIDOSIS

Extracellular deposition of amyloid protein fibrils resulting from a variety of causes (see Table 2.7-20). Classically a disease of older adults.

TABLE 2.7-20. **Types of Amyloidosis**



AMYLOID	CAUSE
AL	A plasma cell dyscrasia with deposition of monoclonal light-chain fragments Associated with multiple myeloma and Waldenström macroglobulinemia
AA	Deposition of the acute-phase reactant serum amyloid A Associated with chronic inflammatory diseases (eg, rheumatoid arthritis), infections, and neoplasms
Dialysis related	Deposition of β_2-microglobulin, which accumulates in patients' joints (scapulohumeral joint and carpal tunnel) on long-term dialysis.
Heritable	Deposition of abnormal gene products (eg, transthyretin, also known as prealbumin). A heterogeneous group of disorders
Senile-systemic	Deposition of otherwise normal transthyretin

AA, Secondary amyloidosis; *AL*, primary amyloidosis.

History/PE

- Clinical presentation depends on the type, amount, and tissue distribution of amyloid. In the most common forms of systemic amyloidosis, primary (AL) and secondary (AA), the major sites of clinically important amyloid deposition are in the kidneys, heart, and liver.
- In some disorders, amyloid deposition is limited to one organ (eg, cerebral amyloid angiopathy in Alzheimer disease).

Diagnosis

Most accurate test: Tissue biopsy with Congo red staining showing apple-green birefringence under polarized light.

Treatment

- Primary amyloidosis is treated with chemotherapy and/or autologous stem cell transplant. Chemotherapy agents are similar to those used in MM.
- Secondary amyloidosis is treated by addressing the underlying condition.

Q 1

A 45-year-old woman presents to the emergency department with fever, chills, nausea, vomiting, and severe flank pain. She has a history of multiple urinary tract infections (UTIs) and was recently hospitalized for pyelonephritis. Urinalysis (UA) reveals pyuria and bacteriuria. Ultrasound performed in the emergency department shows what appears to be a perinephric abscess. What is the next most appropriate step in management?

Q 2

An 80-year-old man is seen in clinic after an incidental finding of elevated IgG on a recent hospital admission for pneumonia. He has no signs of kidney damage, anemia, or bone lesions. The IgG level is 2100 mg/dL, and a subsequent bone marrow biopsy shows 3% plasma cells. What is the next best step?

TRANSPLANT MEDICINE

- Three types of tissue transplantation are increasingly used to treat diseases:
    - **Autologous:** Transplantation from the patient to himself or herself
    - **Allogeneic:** Transplantation from a donor to a genetically different patient
    - **Syngeneic:** Transplantation between identical twins (from a donor to a genetically identical patient)
- With allogeneic donation, efforts are made to ABO- and HLA-match the donor and recipient. Despite matching and immunosuppression, however, transplants may be rejected. There are three types of solid organ rejection: hyperacute, acute, and chronic (see Table 2.7-21).

TABLE 2.7-21. **Types of Solid Organ Transplant Rejection**

VARIABLE	HYPERACUTE	ACUTE	CHRONIC
Timing after transplant	Within minutes (intraoperatively)	Between 5 days and 3 months	Months to years
Pathogenesis	Preformed antibodies	Mixed T-cell and B-cell mediated response against mismatched HLA class I and class II antigens	Chronic immune reaction causing fibrosis
Tissue findings	Vascular thrombi; tissue ischemia	Laboratory evidence of tissue destruction such as ↑ gamma-glutamyl transferase (GGT), alkaline phosphatase, LDH, BUN, or creatinine	Gradual loss of organ function
Prevention	Check ABO compatibility	N/A	N/A
Treatment	Cytotoxic agents	Confirmation with sampling of transplanted tissue; initial treatment with corticosteroids. Additional immunosuppressive therapy can include antilymphocyte antibodies (OKT3), tacrolimus, or mycophenolate mofetil (MMF)	No treatment; biopsy to rule out treatable acute reaction

- Graft-vs-host disease (GVHD) is a complication specific to allogeneic BMT in which donated T cells attack host tissues, especially the skin, liver, and GI tract. It may be acute (<100 days posttransplant) or chronic (>100 days afterward).
  - Minor histocompatibility antigens are thought to be responsible for GVHD, which presents with skin changes, cholestatic liver dysfunction, obstructive lung disease, or GI problems.
- Patients are treated with high-dose corticosteroids.
- Typical posttransplant immunosuppression regimens include prednisone; mycophenolate mofetil (MMF); FK506 (tacrolimus) to suppress immune-mediated rejection; and TMP-SMX, ganciclovir, and fluconazole to prevent subsequent infection in the immunosuppressed host.
- A variant of GVHD is the graft-vs-leukemia effect, in which leukemia patients who are treated with an allogeneic bone marrow transplant have significantly lower relapse rates of leukemia than those treated with an autologous transplant. This difference is thought to be caused by a recognition of leukemia cells by the donor T cells.

1 A

Patients with multiple myeloma frequently have renal dysfunction secondary to urinary immunoglobulins (also known as Bence Jones protein) that have the ability to form casts, leading to cast nephropathy.

2 A

This patient has MGUS, as seen by the elevated IgG in the absence of other clinical abnormalities or symptoms. No treatment is required, but because MGUS can progress to MM, this patient should be seen regularly for signs of renal failure, anemia, or bone pain.

MULTISYSTEM HEMATOLOGY

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Life-threatening state of severe immune system activation due to overactive macrophages and lymphocytes with phagocytosis of blood cells. This commonly occur in infants 0 to 18 months but can be seen in adults of all ages.

History/PE

Presents with fever, rash, hepatosplenomegaly, neurologic disturbances (seizures, mental status changes, ataxia), multiorgan dysfunction, cytopenias, coagulopathies, and hemodynamic instability.

Diagnosis

- Clinical findings as mentioned: ↑ inflammatory markers (ferritin, Scd25, CXCL9)↑
- Bone marrow aspirate demonstrating hemophagocytosis

Treatment

Acutely ill: dexamethasone and etoposide. Supportive care (blood transfusion for anemia and thrombocytopenia), antibiotics for infection due to pancytopenia, immunosuppressive/cytotoxic therapy (eg, dexamethasone and etoposide).

MASTOCYTOSIS

Rare disorder involving excessive release and accumulation of mastocytes in the skin (cutaneous mastocytosis) or other tissues (systemic mastocytosis).

History/PE

Physical examination demonstrating skin findings: diffuse red-brown cutaneous maculopapular lesions and splenomegaly.

Diagnosis

- Skin or bone marrow biopsy with KIT stain (mast cell specific) with ↑ mast cell

concentration, *KIT* mutation, serum tryptase >20.
- Bone marrow biopsy can also show cytopenia due to crowding of the bone marrow by mastocytosis.

Treatment

Aimed at preventing mast cell degranulation with antihistamines, cromolyn, and antileukotrienes.

LANGERHANS CELL HISTIOCYTOSIS

Proliferative disorders of Langerhans cells characterized by histiocyte infiltration of tissue, commonly due to *BRAF* V600E mutation.

History/PE

- Langerhans cell histiocytosis can present with multisystem involvement (eg, skin, lymph nodes, liver, lung, CNS).
- **Skin or oral mucosa:** Can present with eczematous rash (resembles Candida infection) and/or brown, purplish papules.
- **Lung:** Can present with nonproductive cough, dyspnea, chest pain, constitutional symptoms (eg, fever, weight loss).
- **Bone:** Can present with localized bone pain due to osteolytic lesions.
- **CNS:** Can manifest as cognitive dysfunction and ataxia.
- **Diabetes insipidus:** Present with polyuria, nocturia, and polydipsia due to hypothalamic-pituitary axis (HPA) involvement. May also have associated endocrinopathies (hypogonadism, growth failure, impaired glucose tolerance/diabetes mellitus, and thyroid enlargement).

Diagnosis

Bone or skin biopsy, pathology demonstrating collections of histiocytes and Langerhans cells (large ovoid mononuclear cells).

Treatment

Treatment depends on the organ involved in the disease. Bone disease can be treated with curettage or radiotherapy. Skin involvement can be treated with topical steroids or methotrexate. Lymph node involvement can be treated with vinblastine chemotherapy. Steroids can also be considered when the lungs are involved, along with smoking cessation.

HIGH-YIELD FACTS IN

MUSCULOSKELETAL

Whole Body

COMMON ADULT ORTHOPEDIC INJURIES
OTTAWA ANKLE RULES
SALTER-HARRIS PEDIATRIC FRACTURE CLASSIFICATION
COMMON PERIPHERAL NERVE INJURIES
COMPLEX REGIONAL PAIN SYNDROME
OSTEOSARCOMA
SEPTIC ARTHRITIS
OSTEOMYELITIS
OSTEOARTHRITIS
OSTEOPOROSIS
RHEUMATOID ARTHRITIS
SERONEGATIVE SPONDYLOARTHROPATHY
POLYMYOSITIS AND DERMATOMYOSITIS
TEMPOROMANDIBULAR JOINT DISORDERS
MYOFASCIAL PAIN SYNDROME
SYSTEMIC SCLEROSIS
SYSTEMIC LUPUS ERYTHEMATOSUS
SERUM SICKNESS–LIKE REACTION
GIANT CELL ARTERITIS
TAKAYASU ARTERITIS
BEHÇET SYNDROME
FIBROMYALGIA
POLYMYALGIA RHEUMATICA

Upper Extremity

ADHESIVE CAPSULITIS
ROTATOR CUFF INJURIES
COMPARTMENT SYNDROME
RHABDOMYOLYSIS
CARPAL TUNNEL SYNDROME
GANGLION CYST
DUPUYTREN CONTRACTURE
AVASCULAR NECROSIS
RAYNAUD PHENOMENON
HAND INFECTION AND BITE WOUNDS

Lower Extremity

OSTEOCHONDRITIS DISSECANS
BURSITIS
PES ANSERINUS PAIN SYNDROME
PATELLOFEMORAL PAIN SYNDROME
MORTON NEUROMA
GOUT

PSEUDOGOUT

Trunk

LOW BACK PAIN
HERNIATED DISK
SPINAL STENOSIS
SPONDYLOLISTHESIS AND SPONDYLOSIS

WHOLE BODY

COMMON ADULT ORTHOPEDIC INJURIES

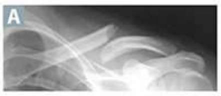
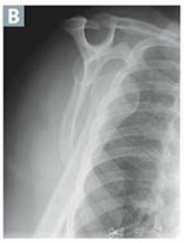
Orthopedic injuries affect all populations and often present as a result of trauma or a fall. Understanding the presenting features, diagnostic findings, and management of these common injuries is critical for developing clinical knowledge. The most commonly tested and seen conditions are discussed here.

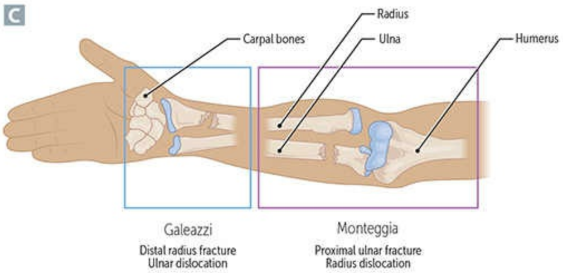
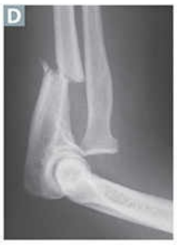
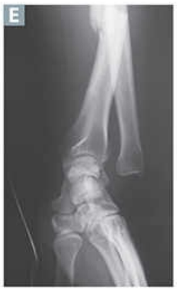
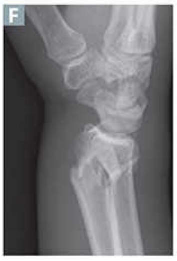
KEY FACT

- Posterior hip dislocation: Shortened, internally rotated leg
- Anterior hip dislocation: Lengthened, externally rotated leg
- Hip fracture: Shortened, externally rotated leg

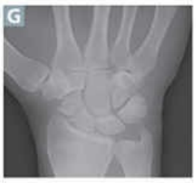
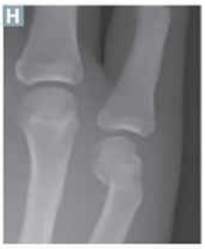
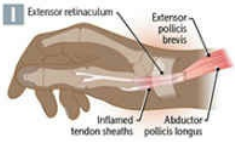
Table 2.8-1 outlines the presentation and treatment of orthopedic injuries that commonly affect adults.

TABLE 2.8-1. Common Adult Orthopedic Injuries

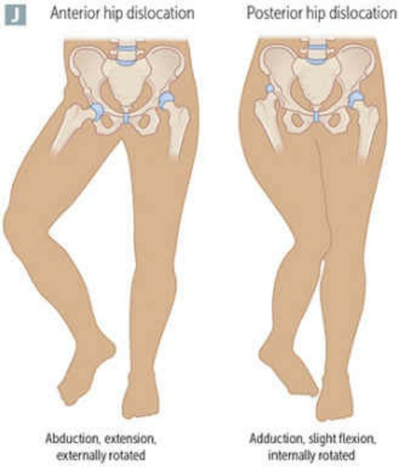
UPPER EXTREMITY		
INJURY	PRESENTATION	TREATMENT
Shoulder and Upper Arm		
Clavicle fracture  	Occurs after trauma (typically a fall). Pain with possible skin tenting due to fracture angulation, proximal fragment will be elevated, distal will be depressed due to muscular pull. There may be accompanying snapping or clicking.	Sling if uncomplicated. Surgery if fracture open, displaced with skin tenting, or neurovascular compromise.
Shoulder dislocation  	Anterior dislocation: Most common (95%); risk for axillary nerve injury. Patients hold arm in slight abduction and external rotation (see Image B). Posterior dislocation: Rare; associated with seizure and electrocution. Patients hold arm in adduction and internal rotation.	Reduction followed by a sling and swath. Recurrent dislocations may need surgery.
Acute rotator cuff tear	Acute-onset anterior shoulder pain and weakness with abduction or external rotation of the humerus after fall on outstretched arm or in young athletes. Significant shoulder stiffness in patients with dermatomyositis. Diagnosis can be made clinically, and it is confirmed with MRI.	Rest and nonsteroidal anti-inflammatory drugs (NSAIDs) for minor injury. Surgery if loss of active range of motion with preserved passive range of motion.
Humerus fracture	Direct trauma. May lead to nerve injury if fractured proximally (axillary), mid-shaft (radial), or distally (median or ulnar).	Coaptation splint if uncomplicated. Surgery if fracture open or significantly displaced.

UPPER EXTREMITY		
INJURY	PRESENTATION	TREATMENT
Forearm		
C  Carpal bones Radius Ulna Humerus Galeazzi Distal radius fracture Ulnar dislocation Monteggia Proximal ulnar fracture Radius dislocation		
"Nightstick fracture"	Ulnar shaft fracture from direct trauma, often in self-defense.	Conservative therapy if uncomplicated. Surgery if open or significant displacement.
Monteggia fracture D 	Diaphyseal fracture of the proximal ulna with subluxation of the radial head. Results from fall on pronated and outstretched arm or in self-defense similar to "nightstick fractures."	Open reduction and internal fixation (ORIF) of the shaft fracture and closed reduction of the radial head.
Galeazzi fracture E 	Diaphyseal fracture of the radius with dislocation of the distal radioulnar joint. Results from a direct blow to the radius.	ORIF of the radius and casting of the fractured forearm in supination to reduce the distal radioulnar joint.
Wrist and Hand		
Colles fracture F 	Distal radius fracture. Results from a fall onto an outstretched hand (FOOSH) that is in dorsiflexion, leading to a dorsally displaced, dorsally angulated fracture. Commonly seen in older adults (osteoporosis) and children.	Closed reduction followed by application of a short arm cast; open reduction if the fracture is open or intra-articular and displaced.

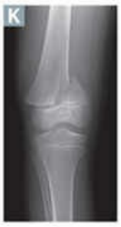
UPPER EXTREMITY

INJURY	PRESENTATION	TREATMENT
Scaphoid fracture G 	Most commonly fractured carpal bone. Results from a FOOSH. May take 2 weeks for x-rays to show fracture. Can assume a fracture if there is tenderness in anatomic snuffbox.	Thumb spica cast, monitor with serial x-rays. If displacement or nonunion present, treatment with ORIF if >1 mm displacement. Possibility for avascular necrosis (AVN) to result from disruption of retrograde blood flow. Risk factors: Proximal, displaced, or comminuted fracture, smoker status.
Boxer's fracture H 	Fracture of the fifth metacarpal neck. Caused by forward trauma of a closed fist (eg, punching a wall).	Closed reduction and splint; surgery if excessively angulated/rotated, unstable, or more than one metacarpal is fractured.
De Quervain tenosynovitis I  Extensor retinaculum Extensor pollicis brevis Inflamed tendon sheaths Abductor pollicis longus	New parent holding infant with outstretched thumb or frequent use of handheld device. Pain on Finkelstein test (flexing thumb across palm and placing the wrist in ulnar deviation).	NSAIDs, ice, and thumb spica splint. Corticosteroid injection if refractory.

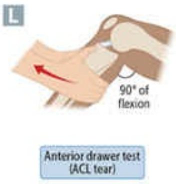
LOWER EXTREMITY

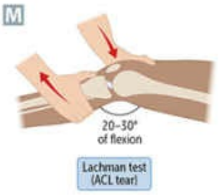
INJURY	PRESENTATION	TREATMENT
Hip and Thigh		
Hip dislocation (see image J)	Posterior dislocation: - Most common (>90%). - Occurs via a posteriorly directed force on an internally rotated, flexed, adducted hip ("dashboard injury"). - Associated with risk for sciatic nerve injury, AVN. Anterior dislocation: Direct blow to an externally rotated, abducted thigh (eg, fall); can injure the obturator nerve.	Emergent closed reduction unless concomitant pathology requiring open reduction. Evaluation with CT scan after reduction. J  Abduction, extension, externally rotated Adduction, slight flexion, internally rotated

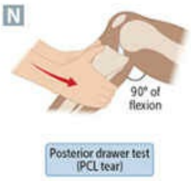
LOWER EXTREMITY

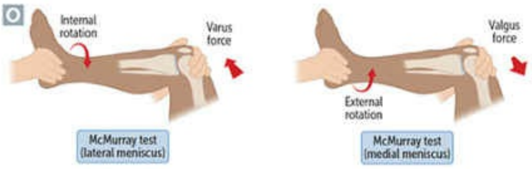
INJURY	PRESENTATION	TREATMENT
Hip fracture	↑ risk with osteoporosis. Presents with shortened and externally rotated leg. Can be radiographically occult, so a good clinical history with ⊖ x-rays warrants further evaluation with CT or MRI. Displaced femoral neck fractures associated with an ↑ risk for AVN and nonunion. Associated with deep venous thrombosis (DVT). Involves acetabulum and/or proximal intracapsular femur.	ORIF. Increased likelihood for displaced femoral neck fracture to require hip hemiarthroplasty or total arthroplasty. Anticoagulation to ↓ the likelihood of DVT.
Femoral fracture K 	Direct trauma. ↑ risk with long-term bisphosphonate use. Complicated by fat emboli: presents with fever, changes in mental status, dyspnea, hypoxia, petechiae, and ↓ platelets.	ORIF. Irrigation and debridement of open fractures.

Knee and Leg

L

90° of flexion
Anterior drawer test (ACL tear)

M

20–30° of flexion
Lachman test (ACL tear)

N

90° of flexion
Posterior drawer test (PCL tear)

O

Internal rotation
Varus force
McMurray test (lateral meniscus)
Valgus force
External rotation
McMurray test (medial meniscus)

Knee ligament injuries	Present with immediate pain, significant swelling, instability, and hematoma. Anterior cruciate ligament (ACL) injury: - Results from a noncontact twisting mechanism, forced hyperextension, or impact to an extended knee. - ⊕ anterior drawer and Lachman tests. - Ruling out of a meniscal or medial collateral ligament (MCL) injury (MCL injury = ⊕ valgus stress test; lateral collateral ligament [LCL] injury = ⊕ varus stress test). Posterior cruciate ligament (PCL) injury: - Results from a posteriorly directed force on a flexed knee (eg, dashboard injury). - ⊕ posterior drawer test. Meniscal tears: - Result from an acute twisting injury or a degenerative tear in older adult patients. - Clicking, catching, or locking possibly present. - Exam showing joint line tenderness and a ⊕ McMurray test. - MRI diagnostic test of choice.	ACL tear: ACL tear is the most commonly repaired ligament in the knee, which is done in symptomatic, young patients. Older patients often treated nonoperatively. Meniscus tear: Repair for younger patients with reparable tears or removal (meniscectomy) if repair fails. Removal in older patients with mechanical symptoms who do not respond to conservative treatment.

LOWER EXTREMITY

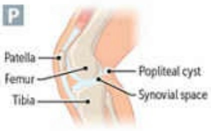
INJURY	PRESENTATION	TREATMENT
Tibial stress fracture	Point tenderness that worsens with activity. Associated with malalignment, foot arch issues, and female athlete triad. Differential diagnosis: Shin splints (medial tibial stress syndrome), which are seen in more casual, overweight athletes and compartment syndrome. Initial x-rays can be negative.	Nonoperative: Activity modification and casting. Operative: Intramedullary nailing versus ORIF (due to increased risk of non-union).
Achilles tendon rupture	Presents with a sudden "pop" in back of calf. More likely with ↓ physical conditioning and ciprofloxacin use. Limited plantar flexion and a ⊕ Thompson test (pressure on the gastrocnemius leading to absent foot plantar flexion).	In elite athletes: Surgery followed by casting (for quicker return to activity). Other cases: Conservative management with casting.
Popliteal (Baker) cyst rupture P  Patella Femur Tibia Popliteal cyst Synovial space	Caused by extrusion of synovial fluid into gastrocnemius or semimembranosus bursa in patients with underlying arthritis. May present with painless bulge in popliteal space, acute calf pain, tibial nerve palsy, or "crescent sign" (ecchymosis at medial malleolus).	Ultrasound to rule out DVT; NSAIDS and activity modification, surgery if remains symptomatic
Ankle and Foot		
Ankle fracture	Falling onto inverted or everted foot. Differential diagnosis: Ankle sprain. Ottawa ankle rules to determine if x-ray is necessary.	ORIF if open, displaced, or unstable.
Calcaneal stress fracture	Pain at the base of posterior foot, reproducible with compression of the calcaneus.	Conservative, including activity modification.
Metatarsal stress fracture	Increased risk with repetitive activities, female athlete triad, or rapid increase in activity (eg, military recruits). Second metatarsal most commonly injured.	Conservative treatment unless fifth metatarsal injured. Due to increased nonunion risk, treated with ORIF or casting.

Image A reproduced with permission from Paladini P, Pellegrini A, Merolla G, et al. Treatment of clavicle fractures. *Transl Med UniSa*. 2012 Jan 18;2:47-58. Images D and E reproduced with permission from Knoop K et al., editors. The Atlas of Emergency Medicine, 3rd ed. New York: McGraw-Hill, 2009, Figs. 11.16, 11.17. Image F reproduced with permission from Usatine RP et al., editors. The Color Atlas of Family Medicine, 2nd ed. New York: McGraw-Hill, 2013, Fig. 103-1. Image H modified with permission from Bohr S, Pallua N. Early Functional Treatment and Modern Cast Making for Indications in Hand Surgery. *Adv Orthop*. 2016;2016:5726979. doi: 10.1155/2016/5726979. Images B, C, G, and I-P reproduced with permission from USMLE-Rx.com.

KEY FACT

The classic unhappy triad of knee injury involves the ACL, the MCL, and the medial meniscus. However, lateral meniscal tears are more commonly seen in acute ACL injuries (see Fig. 2.8-1).

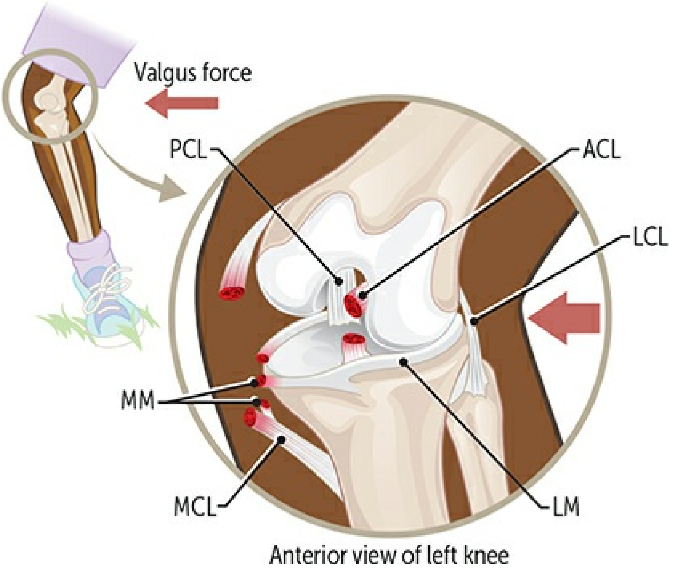

Valgus force
PCL
ACL
LCL
MM
MCL
LM
Anterior view of left knee

FIGURE 2.8-1. The unhappy triad involving the anterior cruciate ligament (ACL), medial meniscus (MM), and medial collateral ligament (MCL) is classically caused by a valgus force at the knee on a planted foot. *LCL*, Lateral collateral ligament; *LM*, lateral meniscus; *PCL*, posterior cruciate ligament. (Reproduced with permission from USMLE-Rx.com.)

OTTAWA ANKLE RULES

A guide for knowing when patients should get an x-ray for their ankle pain vs just "walking it off":

- If patient cannot walk four steps → x-ray

Or:

- X-ray if pain with palpation at the malleolar zone and medial or lateral malleolus (see Fig. 2.8-2)

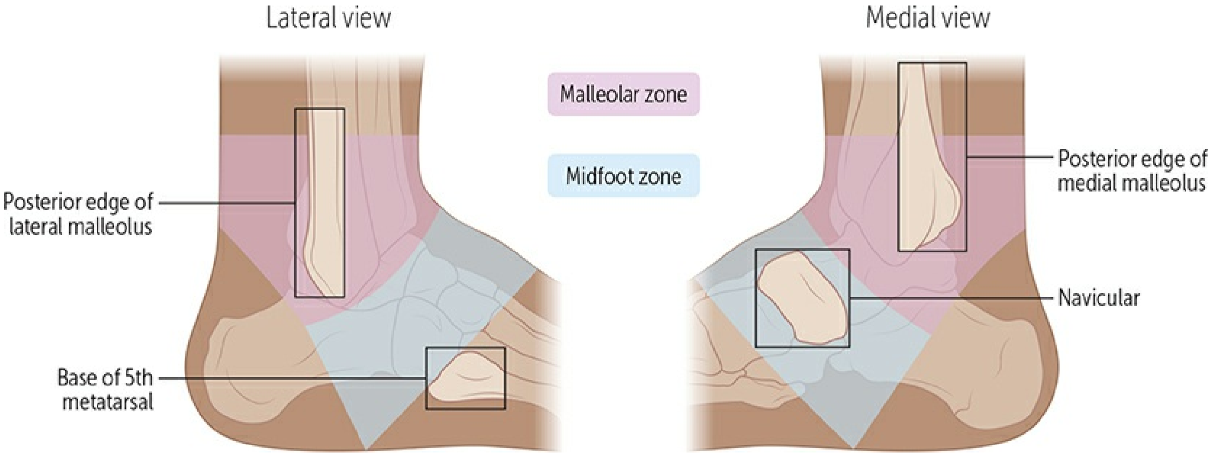

Lateral view
Medial view
Malleolar zone
Midfoot zone
Posterior edge of lateral malleolus
Base of 5th metatarsal
Posterior edge of medial malleolus
Navicular

FIGURE 2.8-2. Zones of the foot and ankle. The highlighted malleolar and lateral midfoot zones are common locations of pain in those who may require an x-ray of their ankle. (Reproduced with permission from USMLE-Rx.com.)

- X-ray of foot if pain at the midfoot and the navicular or proximal metatarsal

SALTER-HARRIS PEDIATRIC FRACTURE CLASSIFICATION

A method for grading fractures in pediatric populations that aids in assessing prognosis of a given fracture in terms of growth arrest (see Fig. 2.8-3):

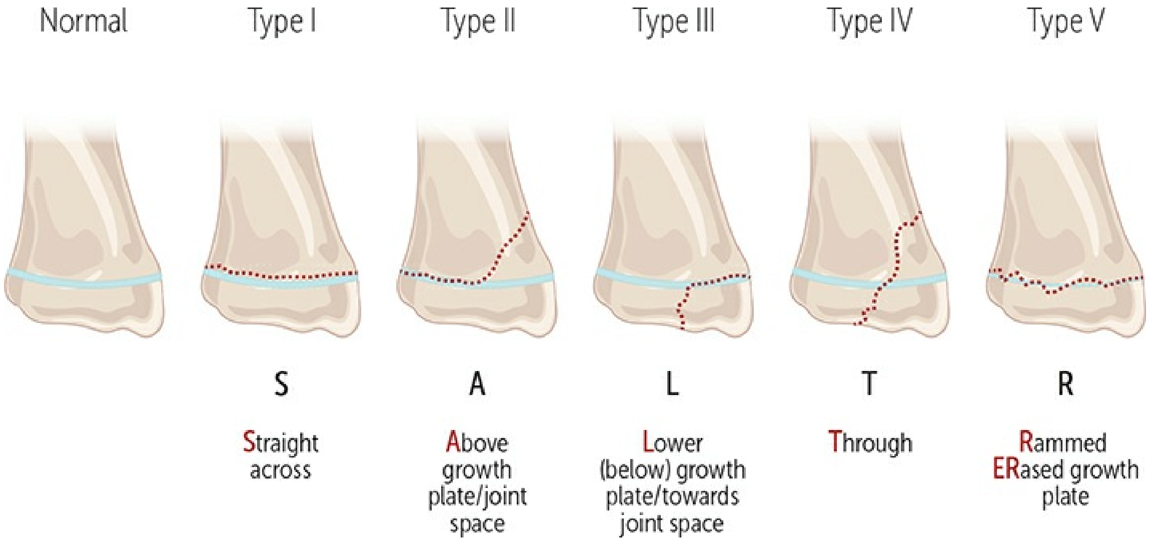

Normal
Type I
Type II
Type III
Type IV
Type V
S
A
L
T
R
Straight across
Above growth plate/joint space
Lower (below) growth plate/towards joint space
Through
Rammed ERased growth plate

FIGURE 2.8-3. The five Salter-Harris fracture classifications are determined by the fracture in relation to the physis. Prognosis differs among the fracture types. (Reproduced with permission from USMLE-Rx.com.)

- Type I: Fracture line is within the growth plate (physis) but has not compressed it (eg, slipped capital femoral epiphysis [SCFE]).
- Type II: Fracture extends through both the metaphysis and physis (most common).
- Type III: Fracture extends through both the physis and epiphysis.
- Type IV: Fracture extends through all three: metaphysis, physis, and epiphysis.
- Type V: The physis is compressed or crushed (worst prognosis, but very rare).

MNEMONIC

“SALTERR”

Slipped
Above
Lower
Through
ERased or **R**ammed

COMMON PERIPHERAL NERVE INJURIES

The brachial plexus and its many nerves are high yield, both as clinical knowledge and commonly tested concepts. Often you will be required to trace symptoms to nerve lesions based on symptoms and exam alone. Table 2.8-2 presents characteristic clinical presentations with their associated nerves.

TABLE 2.8-2. Common Peripheral Nerve Injuries

NERVE	MOTOR DEFICIT	SENSORY DEFICIT	COMMON CAUSES	CLINICAL FINDINGS
Long thoracic	Abduction of arm above 90 degrees	None	Axillary lymphadenectomy, chest tube placement, or stab wound to axilla	Lifting of scapula off thorax when pressing hands against wall, "winged scapula" (Image A)
Radial	Wrist, finger, and thumb extension (Fig. 2.8-4)	Dorsal forearm and hand (first three and a half fingers)	Midshaft humeral fracture Prolonged compression at level of humerus ("Saturday night palsy") (proximal) Radial head subluxation and repetitive pronation/supination (distal)	Wrist drop and sensory deficits (proximal) Finger drop without sensory deficits (distal)
Median	Forearm pronation, wrist and finger flexion, thumb opposition	Palmar surface (first three and a half fingers)	Supracondylar fracture (proximal) Carpal tunnel (distal)	Weak wrist flexion and flat thenar eminence Benediction sign or OK sign (proximal; Fig. 2.8-5) Median claw (distal) when extending fingers

NERVE	MOTOR DEFICIT	SENSORY DEFICIT	COMMON CAUSES	CLINICAL FINDINGS
Ulnar	Finger abduction	Palmar and dorsal surface (last two and a half fingers)	Hook of hamate fracture or Guyon canal syndrome (distal) Elbow dislocation, or entrapment at medial epicondylar groove of humerus (proximal)	Ulnar claw (distal) when extending fingers Lack of finger adduction and abduction
Musculocutaneous	Elbow flexion, forearm supination	Lateral forearm	Shoulder dislocation, trauma to anterior biceps	Absent biceps reflex Weak elbow and shoulder flexion
Axillary	Arm abduction	↓ sensation over the deltoid (regimental badge area)	Anterior shoulder dislocation Fracture of the surgical neck of the humerus	Difficult abduction beyond 15 degrees and flattened deltoid
Common peroneal	Dorsiflexion, eversion	Dorsal foot and lateral leg (Image B)	Knee dislocation, prolonged immobilization (crossed legs), trauma to the fibula	Foot drop
Superior gluteal	Hip abduction	None	Weakness of gluteus medius or minimus muscles	Dropping of contralateral pelvis below horizontal while walking (Trendelenburg sign [Image C])
Tibial	Foot inversion, plantar flexion	Sole of foot (Image D)	Trauma to the knee, Baker cysts	Tarsal tunnel syndrome (distal lesion) Positive Tinel sign at tarsal tunnel
Obturator	Thigh adduction	Distal, medial thigh (Image E)	Pelvic lymph node dissection or tumors	Wide-based gait
Femoral	Hip flexion, knee extension	Anteromedial thigh and medial side of leg and foot (saphenous nerve; Image F)	Direct injury (trauma), prolonged pressure on nerve (eg, lithotomy positioning)	Abnormal knee reflex
Lateral femoral cutaneous	None	Lateral thigh (meralgia paresthetica)	Iatrogenic compression (surgeries, IVC filter replacement), obesity or tight clothing	Abnormal thigh sensation

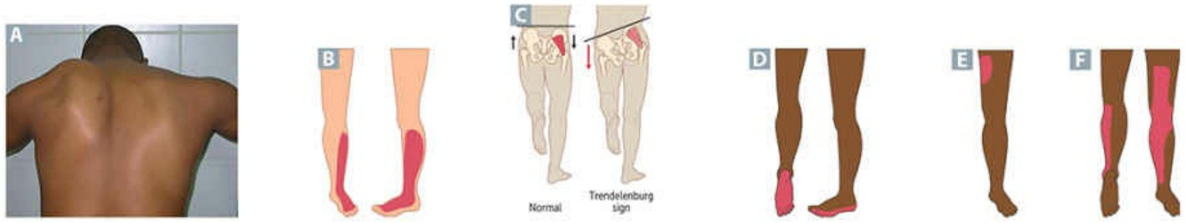


Image A reproduced with permission from Boukhris J, Boussouga M, Jaafar A, Bouslmame N. Stabilisation dynamique d'un winging scapula (à propos d'un cas avec revue de la littérature) [Dynamic stabilization of a winging scapula (about a case with review of the literature)]. *Pan Afr Med J.* 2014;19:331. doi:10.11604/pamj.2014.19.331.3429. Images B–F reproduced with permission from USMLE-Rx.com.

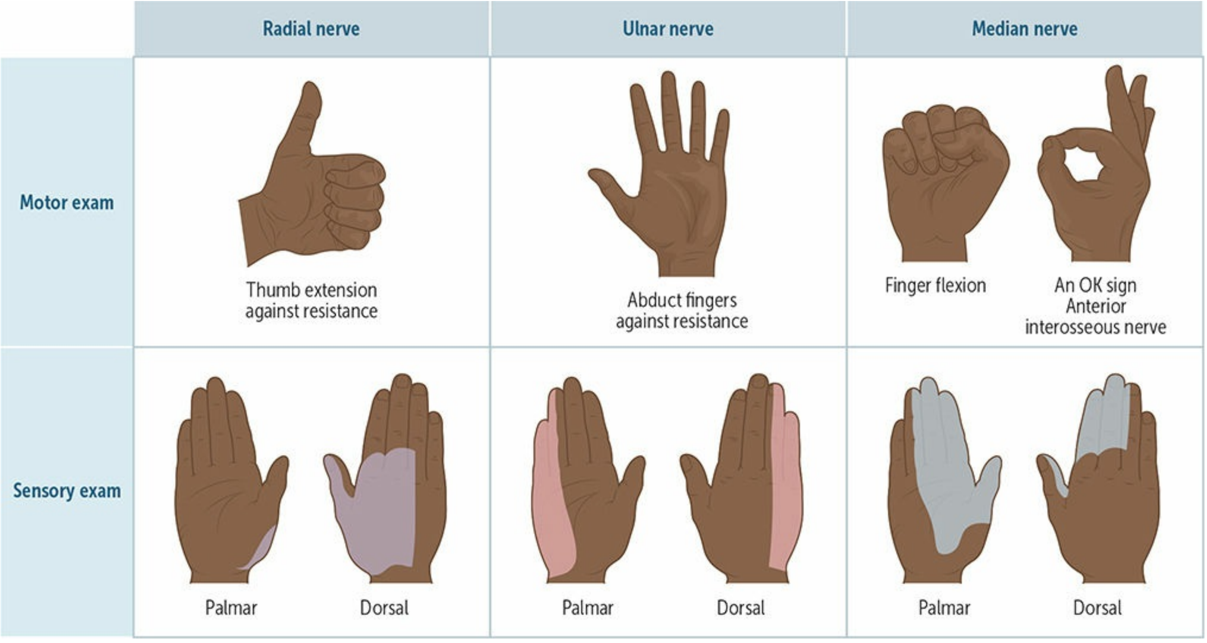

Radial nerve
Ulnar nerve
Median nerve
Motor exam
Thumb extension against resistance
Abduct fingers against resistance
Finger flexion
An OK sign Anterior interosseous nerve
Sensory exam
Palmar
Dorsal
Palmar
Dorsal
Palmar
Dorsal

FIGURE 2.8-4. **Nerve injuries and their respective motor and sensory exam findings.** Radial, median, and ulnar nerve lesions can be distinguished by sensory and motor examinations. (Adapted with permission from USMLE-Rx.com.)

COMPLEX REGIONAL PAIN SYNDROME

A pain syndrome accompanied by loss of function and autonomic dysfunction, usually occurring after trauma. Not linked with true nerve injury.

The disease has three phases:

1) Acute/traumatic: Development of pain → **2) Dystrophic:** Progression of soft tissue edema, muscle wasting → **3) Atrophic:** Limited movement, contracted digits, trophic skin. Radiograph shows severe demineralization of bones.

KEY FACT

Median nerve injury leads to the “benediction sign” caused by an inability to close the first through third digits. Ulnar nerve injury leads to the “claw hand” caused by an inability to open the fourth to fifth digits.

History/PE

- Diffuse pain occurs out of proportion to the initial injury, often in a nonanatomic distribution. Pain is also unrelated to timing of initial injury.
- Loss of function of the affected limb is seen.
- Sympathetic dysfunction occurs and may be documented by skin, soft tissue, or blood flow changes.
- Skin temperature, hair growth, and nail growth may ↑/↓. Edema may be present.

Diagnosis

A clinical diagnosis, but objective evidence of changes in skin hypersensitivity to touch, temperature, changes in color, hair growth, or nail growth.

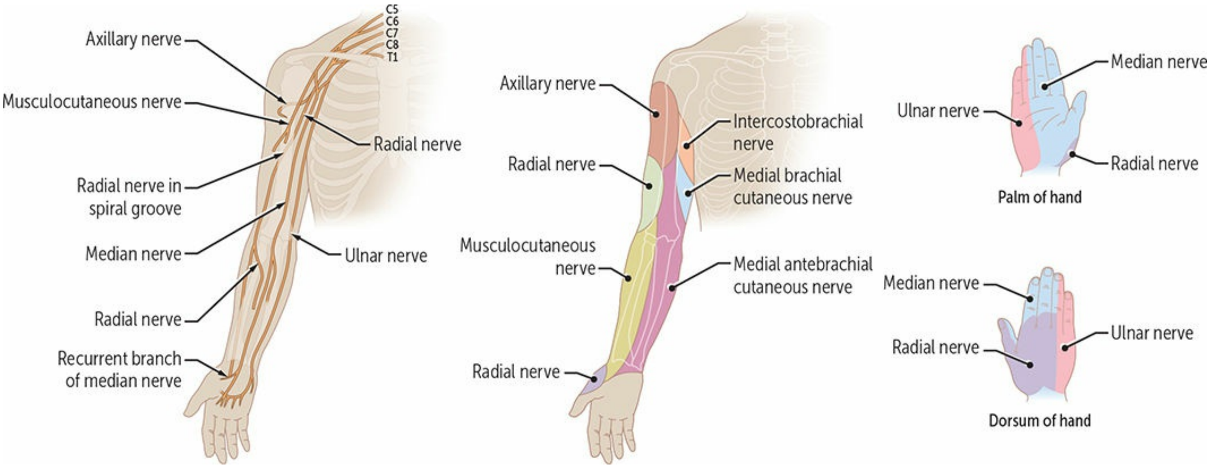

Axillary nerve
Musculocutaneous nerve
Radial nerve in spiral groove
Median nerve
Radial nerve
Recurrent branch of median nerve
C5
C6
C7
C8
T1
Radial nerve
Ulnar nerve
Axillary nerve
Radial nerve
Musculocutaneous nerve
Radial nerve
Intercostobrachial nerve
Medial brachial cutaneous nerve
Medial antebrachial cutaneous nerve
Ulnar nerve
Median nerve
Radial nerve
Palm of hand
Median nerve
Radial nerve
Ulnar nerve
Dorsum of hand

FIGURE 2.8-5. **Comparison of median and ulnar nerve lesions.** Median and ulnar nerve injuries can be distinguished from each other on examination of range of motion. Digit flexion and extension will display classic symptoms for each nerve injury. (Adapted with permission from USMLE-Rx.com.)

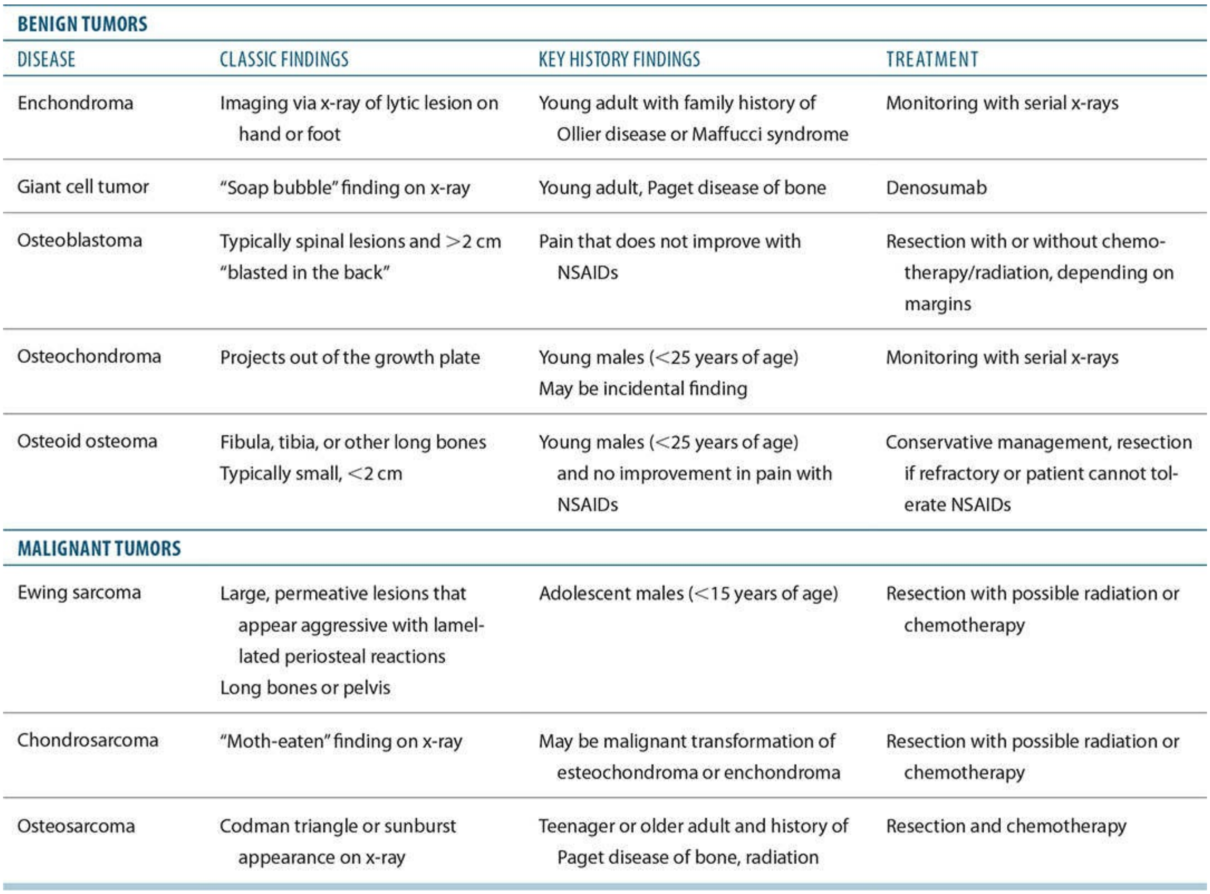
Treatment

- Initial treatment consists of a trial of nonsteroidal anti-inflammatory drugs (NSAIDs) along with physical and occupational therapies.
- Other adjuvant medications include oral corticosteroids, low-dose tricyclic antidepressants, gabapentin, pregabalin, and calcitonin (no oral medications are consistently effective).
- Chemical sympathetic blockade may relieve symptoms.
- Referral to a chronic pain specialist is appropriate for complicated cases.

OSTEOSARCOMA

Although a rare tumor, osteosarcoma is the most common primary malignancy of bone in children and adolescents (Table 2.8-3). It tends to occur in the metaphyseal regions of the distal femur, proximal tibia, and proximal humerus, and it often metastasizes to the lungs. Bimodal age distribution occurs in young adults and patients >65 years of age. Risk factors for older patients are radiation, Paget disease, Li-Fraumeni syndrome, and familial retinoblastoma.

TABLE 2.8-3. **Common Bone Tumors**



DISEASE	CLASSIC FINDINGS	KEY HISTORY FINDINGS	TREATMENT
BENIGN TUMORS			
Enchondroma	Imaging via x-ray of lytic lesion on hand or foot	Young adult with family history of Ollier disease or Maffucci syndrome	Monitoring with serial x-rays
Giant cell tumor	"Soap bubble" finding on x-ray	Young adult, Paget disease of bone	Denosumab
Osteoblastoma	Typically spinal lesions and >2 cm "blasted in the back"	Pain that does not improve with NSAIDs	Resection with or without chemotherapy/radiation, depending on margins
Osteochondroma	Projects out of the growth plate	Young males (<25 years of age) May be incidental finding	Monitoring with serial x-rays
Osteoid osteoma	Fibula, tibia, or other long bones Typically small, <2 cm	Young males (<25 years of age) and no improvement in pain with NSAIDs	Conservative management, resection if refractory or patient cannot tolerate NSAIDs
MALIGNANT TUMORS			
Ewing sarcoma	Large, permeative lesions that appear aggressive with lamellated periosteal reactions Long bones or pelvis	Adolescent males (<15 years of age)	Resection with possible radiation or chemotherapy
Chondrosarcoma	"Moth-eaten" finding on x-ray	May be malignant transformation of esteochondroma or enchondroma	Resection with possible radiation or chemotherapy
Osteosarcoma	Codman triangle or sunburst appearance on x-ray	Teenager or older adult and history of Paget disease of bone, radiation	Resection and chemotherapy

History/PE

- An osteosarcoma manifests with progressive and eventually intractable pain that worsens at night.
- Constitutional symptoms such as fever, weight loss, and night sweats may be present.
- Erythema and enlargement over the site of the tumor may be seen.

Q

A 55-year-old man with a history of prostate cancer presents with low back pain (LBP) and bilateral leg weakness. On examination, he is found to have point tenderness on the lumbar spine and ↓ sensation in his legs. What is the best next step?

Diagnosis

- **Best initial test:** X-rays. These can show a Codman triangle (formation of periosteal new bone at the diaphyseal end of the lesion) or a "sunburst" pattern of the osteosarcoma (see Fig. 2.8-6) in contrast with both the multilayered "onion skinning" that is classic for Ewing sarcoma and the "soap bubble" appearance of giant cell tumor of bone (see Fig. 2.8-7).

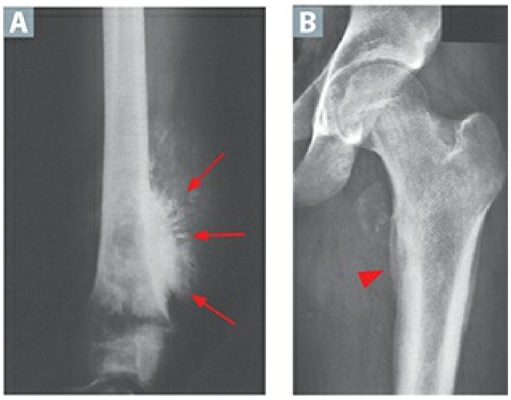


FIGURE 2.8-6. **Malignant bone tumors. (A)** Osteosarcoma. X-ray of the femur shows the typical “sunburst” appearance *(arrows)*. **(B)** Ewing sarcoma. X-ray of the left hip shows characteristic “onion skinning” in proximal femur *(arrowhead)*.(Reproduced with permission from Kantarjian HM, et al. *MD Anderson Manual of Medical,* 1st ed. New York, NY: McGraw-Hill; 2006.)

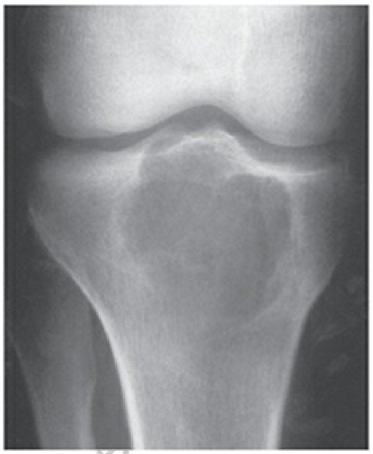


FIGURE 2.8-7. **Giant cell tumor of the bone.** Note the “soap bubble” appearance at the proximal end of the tibia. (Reproduced with permission from Skinner HB. *Current Diagnosis & Treatment in Orthopedics,* 4th ed. New York, NY: McGraw-Hill; 2006.)

- **Most accurate test:** Bone biopsy.
- MRI and positron emission tomography (PET)/CT or bone scan for staging and workup.

KEY FACT

The most common benign bone tumor is an osteochondroma. It commonly presents as a painless mass and does not typically require treatment—just serial monitoring with x-rays.

A

The best next step would be to obtain an MRI. MRI is the best study, but preventing permanent neurologic disability is the priority. Remember to consider multiple myeloma, which can present almost identically. Treatment is to administer steroids to relieve spinal cord compression resulting from likely bone metastasis.

Treatment

- Limb-sparing surgical procedures and preoperative and postoperative chemotherapy (eg, methotrexate, doxorubicin, cisplatin, ifosfamide)

- Amputation possibly necessary

SEPTIC ARTHRITIS

An infection of the joint space that typically occurs after open injury or bacteremia.

History/PE

Presents as a warm, red, immobile joint. Palpable effusions may also be present. Fevers and chills can be seen if the patient is bacteremic. Intense pain with brief joint movement (short arc sign) is pathognomonic. Typically unable to bear weight. Prosthetic joints greatly ↑ risk. Other risk factors include recent trauma, underlying joint disease (eg, gout, rheumatoid arthritis, or osteoarthritis), older age, recent articular injection, and bacteremia from endocarditis or intravenous (IV) drug use.

Diagnosis

- **Most accurate test:** Joint aspiration. See Table 2.8-4 and Figure 2.8-8

TABLE 2.8-4. Synovial Fluid Analysis

	NORMAL	NONINFLAMMATORY	INFLAMMATORY[a]	SEPTIC
Color	Clear	Yellow	Yellow	Yellow-green
Viscosity	High	High	Low	Variable
WBC (per mm³)	<200	0–1000	1000–10,000 (up to 100,000)	10,000–100,000
Polymorphonuclear (PMN) leukocytes (%)	<25	<25	≥50	≥75
Glucose (mg/dL)	= serum	= serum	>25 (crystal analysis for gout vs pseudogout)	<25

[a] A joint affected by inflammatory arthritis can become secondarily infected.

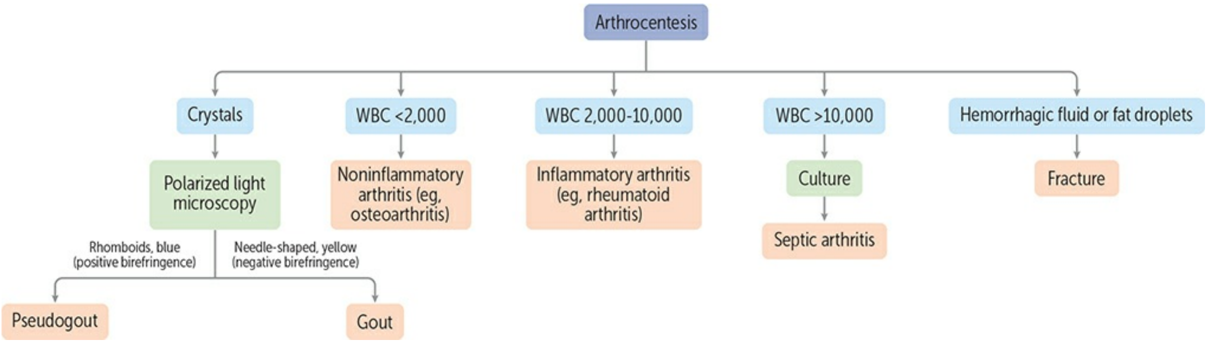

Arthrocentesis
Crystals
WBC <2,000
WBC 2,000-10,000
WBC >10,000
Hemorrhagic fluid or fat droplets
Polarized light microscopy
Noninflammatory arthritis (eg, osteoarthritis)
Inflammatory arthritis (eg, rheumatoid arthritis)
Culture
Fracture
Septic arthritis
Rhomboids, blue (positive birefringence)
Needle-shaped, yellow (negative birefringence)
Pseudogout
Gout

FIGURE 2.8-8. Synovial fluid characteristics. Diagnosis of inflammatory pathology can be done utilizing arthrocentesis and fluid analysis. Color, crystal content, and the quantity of WBCs can determine the appropriate diagnosis. (Reproduced with permission from USMLE-Rx.com.)

- **Septic arthritis:** WBC count >50,000/mm^3, ⊕ gram stain, or ⊕ fluid culture
- **Most common organisms:** *Staphylococcus*, *Streptococcus*, and gram ⊖ rods (see Table 2.8-5)

TABLE 2.8-5. Common Septic Arthritis Etiologies

BACTERIA	RISK FACTORS/HISTORY	TREATMENT
Staphylococcus aureus	Middle-aged or older adult	Vancomycin
Neisseria gonorrhoeae	Young adult, sexually active; due to disseminated gonococcal infection via hematogenous spread "STD" — synovitis, tenosynovitis, and dermatitis	Third-generation cephalosporin
Haemophilus influenzae	Age <2 years of age, sickle cell	Third-generation cephalosporin
Salmonella	Sickle cell	Third-generation cephalosporin

Treatment

Empiric ceftriaxone and vancomycin initially until culture test results; then modification of therapy for specific organisms. Septic arthritis is considered a surgical emergency. Septic joints are considered surgical emergencies and are treated with joint drainage or debridement. Delay in treatment may lead to permanent joint destruction.

KEY FACT

Any patient presenting with a red, hot, and swollen joint should have joint aspiration/arthrocentesis to rule out septic arthritis.

Q

A 15-year-old youth presents with several months' history of pain in the upper part of his thigh. The pain is worse at night. A plain film shows a small lucent nidus. What over-the-counter (OTC) remedy is indicated?

KEY FACT

In sexually active individuals with joint pain, consider the diagnosis of gonococcal septic arthritis. *Neisseria gonorrhoeae* septic arthritis can present with asymmetric oligoarthritis, tenosynovitis, and skin rash.

OSTEOMYELITIS

Bone infection caused by direct spread from a soft tissue infection (80% of cases) is most common in adults, whereas infection caused by hematogenous seeding (20% of cases) is more common in children (metaphysis of the long bones) and patients who use injectable drugs (vertebral bodies). Common pathogens are outlined in Table 2.8-6. Patient characteristics are important to keep in mind, as they can clue you in to commonly associated pathogens.

TABLE 2.8-6. Common Pathogens in Osteomyelitis

IF...	THINK...
No risk factors	*Staphylococcus aureus*
IV drug use	*S aureus* or *Pseudomonas*
Sickle cell disease	*Salmonella*
Hip replacement	*Staphylococcus epidermidis* (coagulase ⊖ staphylococcus)
Foot puncture wound	*Pseudomonas*
Chronic	*S aureus*, *Pseudomonas*, Enterobacteriaceae
Diabetes mellitus	Polymicrobial, *Pseudomonas*, *S aureus*, streptococci, anaerobes

History/PE

Presents with localized bone pain and tenderness along with warmth, swelling, erythema, and limited motion of the adjacent joint. Systemic symptoms (fevers, chills) and purulent drainage may be present.

KEY FACT

Osteomyelitis in patients with diabetes should be treated with antibiotics targeting gram ⊕ organisms and anaerobes.

A

This adolescent patient is likely presenting with osteoid osteoma, a benign bone-forming tumor characterized by prostaglandin formation. Relief of pain is thus often achieved with NSAIDs. Tumors may resolve on their own, but surgical removal of the nidus may be necessary for symptom relief.

Diagnosis

- **Labs:** ↑ WBC count; ↑ erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels in most cases. Blood cultures may be ⊕.
- **Imaging:**
  - X-rays are often ⊖ initially but may show periosteal elevation within 10 to 14 days. Bone scans are sensitive for osteomyelitis but lack specificity.
  - MRI (the test of choice) will show ↑ signal in the bone marrow and associated soft tissue infection (see Fig. 2.8-9).

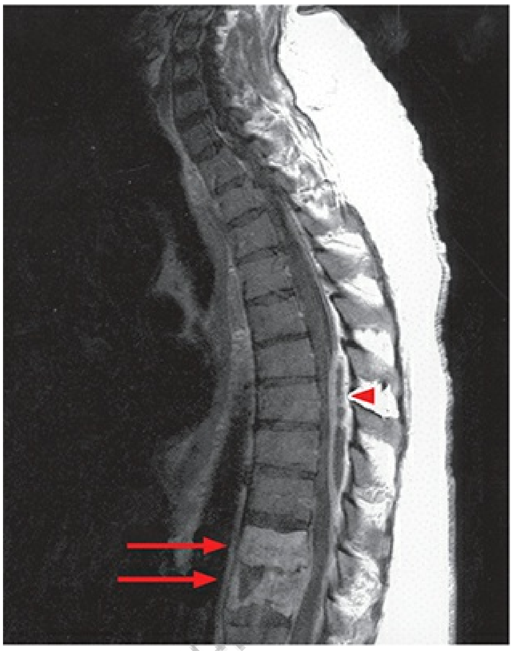


FIGURE 2.8-9. Diskitis/osteomyelitis. Sagittal contrast-enhanced MRI shows destruction of a lower thoracic intervertebral disk with abnormal enhancement throughout the adjacent vertebral bodies *(arrows)* and a posterior rim-enhancing epidural abscess *(arrowhead)* in the spinal canal. (Reproduced with permission from Tintinalli JE et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide,* 6th ed. New York, NY: McGraw-Hill; 2004.)

  - **Most accurate test:** Bone aspiration with Gram stain and culture. However, clinical diagnosis made by probing through the soft tissue to bone is usually sufficient, as aspiration carries a risk for infection.

Treatment

- **Most accurate treatment:** Surgical debridement of necrotic, infected bone followed by IV antibiotics for 4 to 6 weeks. Empiric antibiotic selection is based on the suspected organism and Gram stain.
- The physician should consider clindamycin plus ciprofloxacin, ampicillin/sulbactam, or oxacillin/nafcillin (for methicillin-sensitive *Staphylococcus aureus*); vancomycin (for methicillin-resistant *S aureus* [MRSA]); or ceftriaxone or ciprofloxacin (for gram ⊖ bacteria).

Complications

Chronic osteomyelitis, sepsis, septic arthritis. Long-standing chronic osteomyelitis with a draining sinus tract may eventually lead to squamous cell carcinoma (Marjolin ulcer).

KEY FACT

Penicillin and cephalosporins have minimal cross-reactivity. If a patient had an allergic rash to penicillin, cephalosporins are considered safe. If a patient had an anaphylactic reaction or developed angioedema while on penicillin, use a non–β-lactam antibiotic.

Q

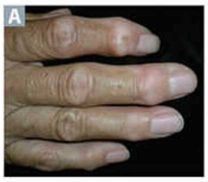
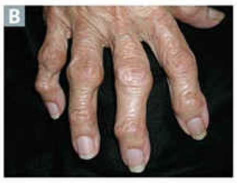
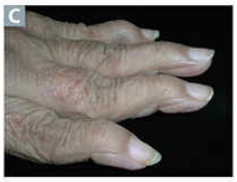
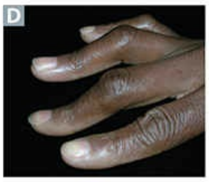
An 11-year-old boy with a history of multiple hospitalizations for pain crises, all related to his sickle cell anemia, presents with fever and severe pain in his right hand. Physical examination shows an area of redness, tenderness, and swelling near the right second metacarpal. Laboratory results show leukocytosis and an elevated erythrocyte sedimentation rate (ESR). MRI shows an area of ↑ intensity in the painful area. What pathogen is the most likely cause of his condition?

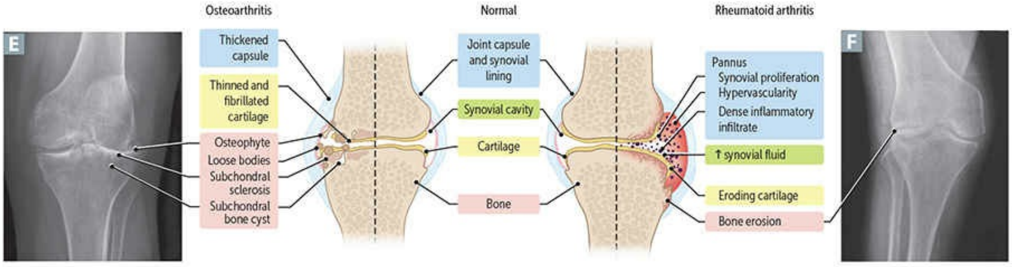
OSTEOARTHRITIS

A common chronic, noninflammatory arthritis of the synovial joints. Characterized by deterioration of the articular cartilage and osteophyte bone formation at the joint surfaces. Risk factors include age, female sex, prior joint trauma, malalignment, sedentary lifestyle, ⊕ family history, obesity, and a history of joint trauma. Osteoarthritis (OA) is considered primary if no underlying etiology is found. Secondary OA may be due to prior trauma, avascular necrosis (AVN), inflammatory arthritis, osteochondritis dissecans, and more.

Table 2.8-7 contrasts OA with rheumatoid arthritis (RA).

TABLE 2.8-7. Osteoarthritis vs Rheumatoid Arthritis

VARIABLE	OSTEOARTHRITIS	RHEUMATOID ARTHRITIS
History	Affects older adults Slow onset Pain that worsens with use	Affects the young Prolonged morning stiffness that improves with use
Joint involvement	Affects the distal interphalangeal (DIP) joint, proximal interphalangeal (PIP) joint, first carpometacarpal (CMC) joint, hips, and knees (see Images A and B) Symmetric if affecting hands but classically asymmetric elsewhere  	Affects the wrists, metacarpophalangeal (MCP) joint, ankles, knees, shoulders, hips, and elbows (see Images C and D) Symmetric distribution  
Synovial fluid analysis and imaging	WBC count <2000 cells/mm³; osteophytes X-ray showing joint space narrowing (see Image E)	WBC count between 2000 and 50,000 cells/mm³ (see Image F)
Treatment	Physical therapy, NSAIDs, intra-articular corticosteroid injections, and surgery	Disease-modifying antirheumatic drugs (DMARDs) with NSAIDs or glucocorticoids for symptom flares or while bridging to DMARD therapy


Osteoarthritis
Normal
Rheumatoid arthritis
E
Thickened capsule
Thinned and fibrillated cartilage
Osteophyte
Loose bodies
Subchondral sclerosis
Subchondral bone cyst
Joint capsule and synovial lining
Synovial cavity
Cartilage
Bone
Pannus
Synovial proliferation
Hypervascularity
Dense inflammatory infiltrate
↑ synovial fluid
Eroding cartilage
Bone erosion
F

Arthritis illustration and Image A reproduced with permission from USMLE-Rx.com. Image B reproduced with permission from Clement ND, Breusch SJ, Biant LC. Lower limb joint replacement in rheumatoid arthritis. *J Orthop Surg Res.* 2012;7:27. Published 2012 Jun 14. doi:10.1186/1749-799X-7-27. Images C, D, E, and F reproduced with permission from Dr. Richard Usatine.

History/PE

Presents with crepitus, ↓ range of motion (ROM), and initially pain that worsens with activity and weight-bearing but improves with rest. Morning stiffness generally lasts for <30 minutes. Stiffness is also experienced after periods of rest (“gelling”). Bony nodes occurring on distal interphalangeal (DIP) joints in the hands are called “Heberden nodes,” and the ones on the proximal interphalangeal (PIP) joints are referred to as “Bouchard nodes.”

A

Salmonella is the most likely pathogen causing the patient’s condition. *Staphylococcus aureus* is the most common cause in patients without sickle cell disease and is the second most common organism that causes osteomyelitis in patients with sickle cell disease.

KEY FACT

There is a minimal role for opioids in the treatment of osteoarthritis because potential risks outweigh benefits. If patients have refractory, severe pain and are unwilling or unable to undergo surgical treatment, opioids may be considered. Weak opioids (eg, tramadol) are preferred for initial treatment.

Diagnosis

- X-rays show joint space narrowing, osteophytes, subchondral sclerosis, and subchondral bone cysts (see Fig. 2.8-10). X-ray severity does not correlate with symptomatology.

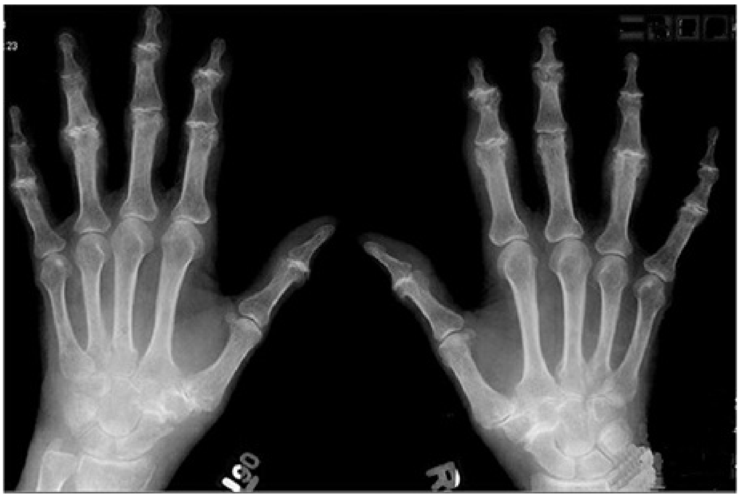


FIGURE 2.8-10. Osteoarthritis. Plain x-rays show joint space narrowing, osteophytes, and subchondral degenerative cysts involving the DIP and PIP joints, with sparing of the MCP. (Reproduced with permission from USMLE-Rx.com.)

- Laboratory tests, including inflammatory markers, are typically normal.

Treatment

- **Best initial treatment:** Physical therapy, weight reduction (if comorbid obesity present), and NSAIDs. Intra-articular corticosteroid injections may provide temporary relief.
- **Most definitive treatment:** Surgery—consider joint replacement (eg, total hip/knee/shoulder arthroplasty) in advanced cases. Patients are at higher risk for developing osteoporosis.

OSTEOPOROSIS

Refer to Endocrinology chapter.

RHEUMATOID ARTHRITIS

A systemic autoimmune disorder characterized by chronic, destructive, inflammatory arthritis with symmetric joint involvement resulting in synovial hypertrophy and pannus formation, ultimately leading to erosion of adjacent cartilage, bone, and tendons. Risk factors include female sex, 35 to 50 years of age, smoking, and human leukocyte antigen (HLA)–death receptor (DR)4.

KEY FACT

Keratoconjunctivitis sicca secondary to Sjögren syndrome is a common ocular manifestation of RA.

History/PE

- Insidious onset of prolonged morning stiffness (>30 minutes) occurs along with painful, warm swelling of polyarticular symmetric joints (wrists; metacarpophalangeal [MCP] joints; PIP joints of hands, ankles, knees, shoulders, hips, and elbows) for >6 weeks.
- Rheumatoid nodules may form at bony prominences and near joints affected by the disease.
- In advanced disease, ulnar deviation of the fingers is seen with MCP joint hypertrophy.
- RA also presents with ligament and tendon deformations (eg, swan-neck and boutonnière deformities), vasculitis, atlantoaxial subluxation (↑ intubation risk), and keratoconjunctivitis sicca (if accompanying Sjogren syndrome is present). RA typically spares the lumbosacral spine.

KEY FACT

RA-Associated Syndromes
Felty syndrome: RA, splenomegaly, and neutropenia
Caplan syndrome: RA, pneumoconiosis, and lung nodules

KEY FACT

The DIP joint is spared in RA compared to OA and psoriatic arthritis, where the DIP is involved.

Diagnosis

- **Diagnostic criteria** (need ≥6 points):
  - ↑ rheumatoid factor (RF) (IgM antibodies against Fc IgG) or the presence of anti-CCP (cyclic citrullinated peptide) antibodies (1 point)
  - ↑ ESR or CRP (1 point)
  - Inflammatory arthritis of three or more joints (up to 5 points)
  - Symptom duration >6 weeks (1 point)
  - Exclusion of diseases with similar clinical presentations such as psoriatic arthritis, gout, pseudogout, and systemic lupus erythematosus (SLE)
- **Labs:**
  - ↑ ESR and CRP (nonspecific signs of inflammation); anemia of chronic disease is common.
  - Synovial fluid aspirate showing turbid fluid, ↓ viscosity, and an ↑ WBC count (2000–50,000 cells/μL)
- **X-rays** (not necessary to confirm RA):
  - **Early:** Soft tissue swelling and juxta-articular demineralization
  - **Late:** Symmetric joint space narrowing and erosions

Treatment

- Disease-modifying antirheumatic drugs (DMARDs) should be started early. They include methotrexate (initial drug of choice), hydroxychloroquine, and sulfasalazine. Second-line agents include tumor necrosis factor (TNF) inhibitors, rituximab (anti-CD20), and leflunomide.

- NSAIDs or glucocorticoids can be used for symptom flares or while bridging to DMARD therapy.

KEY FACT

Hydroxychloroquine causes irreversible retinal toxicity. Patients must undergo regular screening while taking this medication for long periods (>5 years) to look for findings indicative of toxicity (“bull’s-eye” appearance).

Complications

- **Articular manifestations:** Joint deformation, osteopenia, OA
- **Extra-articular manifestations:** Anemia, rheumatoid nodules, scleritis, amyloidosis, cardiovascular disease, vasculitis, lung fibrosis, Caplan syndrome, carpal tunnel syndrome, Sjögren syndrome, and Felty syndrome

SERONEGATIVE SPONDYLOARTHROPATHY

Ankylosing Spondylitis

A chronic inflammatory disease of the spine and pelvis that leads to erosion and fusion of the sacroiliac joint. Strongly associated with HLA-B27. Risk factors include male sex and a ⊕ family history.

History/PE

- Typical onset is in the late teens and early 20s. It presents with fatigue, intermittent hip pain, and low back pain that worsens with inactivity and at night and improves with activity.
- ↓ spine flexion (⊕ Schober test), loss of lumbar lordosis, hip pain, and stiffness increase as the disease progresses. Vertebral fracture may occur after minimal trauma.
- Ankylosing spondylitis (AS) can also be associated with anterior uveitis, aortic insufficiency, psoriasis, inflammatory bowel disorder (IBD), and heart block.
- Approximately 30% of AS cases are associated with enthesitis (pain at insertion of tendons/ligaments) at the heel (Achilles tendon involvement) and dactylitis (diffuse swelling of toes/fingers, named “sausage digits”).
- Other seronegative spondyloarthropathies must be ruled out (also associated with HLA-B27), including the following:
    - Reactive arthritis: A disease of young adults. The characteristic arthritis, uveitis, conjunctivitis, and urethritis usually follow an infection with *Campylobacter* (especially *C jejuni*), *Shigella*, *Salmonella*, *Yersinia*, *Chlamydia*, or *Ureaplasma*.
    - Psoriatic arthritis: An oligoarthritis that can include the DIP joints. Associated with psoriatic skin changes and sausage-shaped digits (dactylitis). X-rays show a classic erosion and resorption of periarticular bone, also called a “pencil-in-cup” deformity (arrows in Fig. 2.8-11).

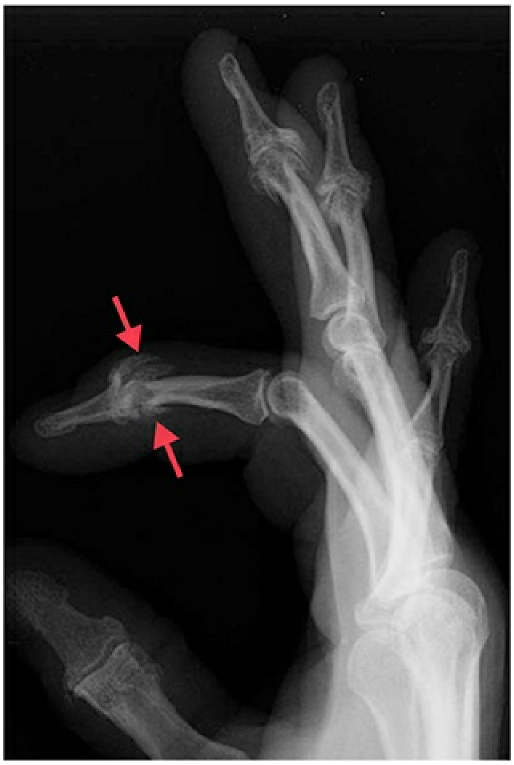


FIGURE 2.8-11. In those with psoriatic arthritis, the middle phalanx may be pointed on x-ray and appear to be rubbing away at the distal phalanx, giving an appearance of a pencil in a cup. (Reproduced with permission from Dr. Richard Usatine.)

- Enteropathic spondylitis: An AS-like disease characterized by sacroiliitis that is usually asymmetric and is associated with IBD.

KEY FACT

Keratoderma blennorrhagica (skin lesions on palms and soles) and circinate balanitis (painless ulcerative lesion on glans penis) are characteristic cutaneous features of reactive arthritis.

MNEMONIC

Reactive arthritis—

"Can't see (uveitis), can't pee (urethritis), can't climb a tree (arthritis)."

Diagnosis

Best initial test: X-rays may show erosion, ankylosis, fusion, or sclerosis of sacroiliac joints; squaring of the lumbar vertebrae; development of vertical syndesmophytes (ossification of spinal ligament); and bamboo spine (see Fig. 2.8-12).

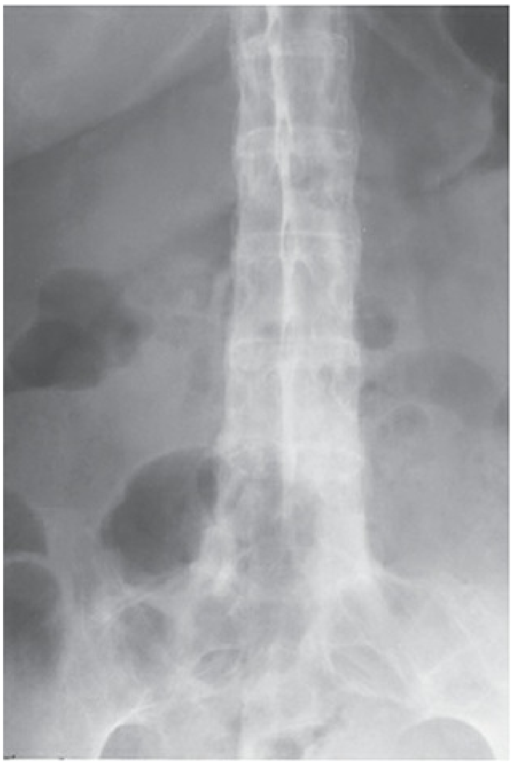


FIGURE 2.8-12. **Ankylosing spondylitis.** Frontal view of the thoracolumbar spine shows the classic “bamboo” appearance of the spine, which results from fusion of the vertebral bodies and posterior elements. (Reproduced with permission from Chen MY et al. *Basic Radiology,* 2nd ed. New York, NY: McGraw-Hill; 2011.)

Laboratory values:

- ⊕ HLA-B27 found in 85% to 95% of cases
- ESR or CRP ↑ in 85% of cases
- ⊖ RF; ⊖ antinuclear antibody (ANA)

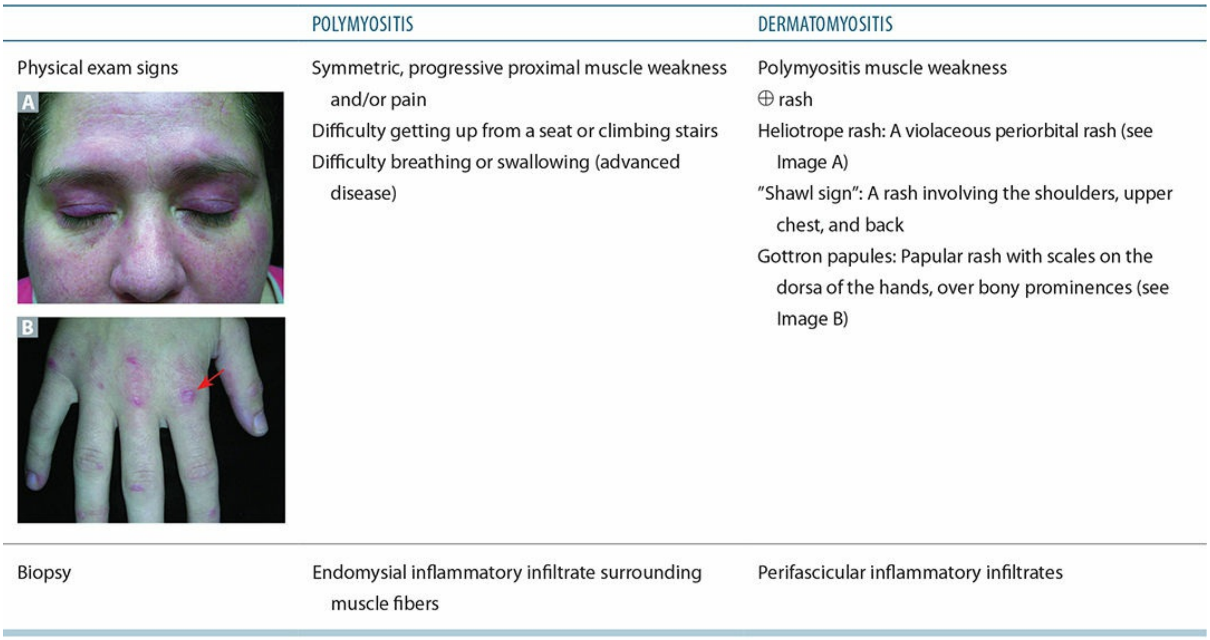
Treatment

- **Best initial therapy:** NSAIDs for pain; exercise to improve posture and breathing
- TNF inhibitors, interleukin (IL)-17 inhibitors, or sulfasalazine in refractory cases

POLYMYOSITIS AND DERMATOMYOSITIS

Both diseases are progressive immune-mediated myopathies characterized by striated muscle inflammation manifesting as symmetric proximal muscle weakness. Polymyositis presents with muscle weakness; dermatomyositis is differentiated by cutaneous involvement. They most often affect patients 50 to 70 years of age; the male-to-female ratio is 1:2. Black individuals are affected more often than White individuals (see Table 2.8-8).

TABLE 2.8-8. **Polymyositis vs Dermatomyositis**



	POLYMYOSITIS	DERMATOMYOSITIS
Physical exam signs	Symmetric, progressive proximal muscle weakness and/or pain Difficulty getting up from a seat or climbing stairs Difficulty breathing or swallowing (advanced disease)	Polymyositis muscle weakness ⊕ rash Heliotrope rash: A violaceous periorbital rash (see Image A) "Shawl sign": A rash involving the shoulders, upper chest, and back Gottron papules: Papular rash with scales on the dorsa of the hands, over bony prominences (see Image B)
Biopsy	Endomysial inflammatory infiltrate surrounding muscle fibers	Perifascicular inflammatory infiltrates

Images reproduced with permission from Dr. Richard Usatine.

History/PE

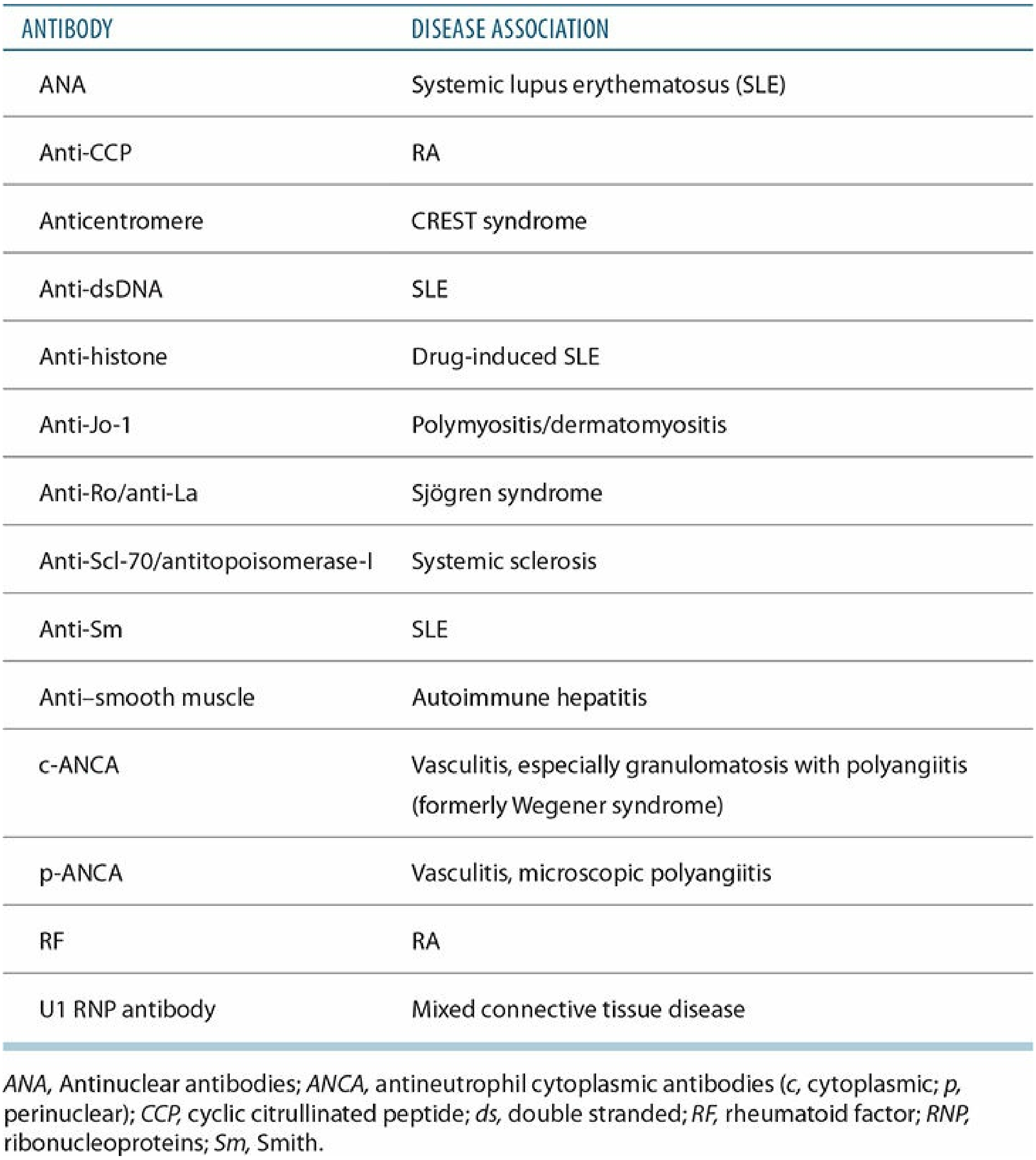
See Table 2.8-8.

- Ten percent of polymyositis/dermatomyositis cases are associated with interstitial lung disease (ILD).
- Esophageal involvement presents as dysphagia.
- Cardiac involvement presents as myocarditis and cardiac conduction deficits.
- Polymyositis/dermatomyositis can be associated with an underlying malignancy, especially lung, breast, and ovarian carcinoma. Dermatomyositis is associated with ↑ rate of malignancy compared with PM.

Diagnosis

- Based on characteristic clinical presentation and laboratory values
- **Best initial test:** ↑ serum creatine kinase and anti-Jo-1 antibodies (see Table 2.8-9)

TABLE 2.8-9. Common Antibodies and Their Autoimmune Disease Associations



ANTIBODY	DISEASE ASSOCIATION
ANA	Systemic lupus erythematosus (SLE)
Anti-CCP	RA
Anticentromere	CREST syndrome
Anti-dsDNA	SLE
Anti-histone	Drug-induced SLE
Anti-Jo-1	Polymyositis/dermatomyositis
Anti-Ro/anti-La	Sjögren syndrome
Anti-Scl-70/antitopoisomerase-I	Systemic sclerosis
Anti-Sm	SLE
Anti–smooth muscle	Autoimmune hepatitis
c-ANCA	Vasculitis, especially granulomatosis with polyangiitis (formerly Wegener syndrome)
p-ANCA	Vasculitis, microscopic polyangiitis
RF	RA
U1 RNP antibody	Mixed connective tissue disease

ANA, Antinuclear antibodies; *ANCA,* antineutrophil cytoplasmic antibodies (*c,* cytoplasmic; *p,* perinuclear); *CCP,* cyclic citrullinated peptide; *ds,* double stranded; *RF,* rheumatoid factor; *RNP,* ribonucleoproteins; *Sm,* Smith.

- **Most accurate test:** Muscle biopsy to differentiate between polymyositis and dermatomyositisin atypical presentations

KEY FACT

Aldolase, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) are also muscle enzymes. In patients with unexplained elevation of AST and ALT (not due to alcohol abuse or liver disease) and especially if AST > ALT, creatine kinase (CK) should be checked to evaluate for myopathy.

Treatment

- **Best initial treatment:** High-dose corticosteroids (eg, prednisone) with taper after 4 to 6 weeks to ↓ the maintenance dose

- Azathioprine and/or methotrexate used in steroid-resistant or intolerant cases

TEMPOROMANDIBULAR JOINT DISORDERS

Several factors contribute to the development of temporomandibular joint (TMJ) disorders, including joint trauma (eg, bruxism) and history of psychiatric illness (eg, depression, anxiety).

History/PE/Diagnosis

- Patients present with unilateral morning heading and with waxing and waning facial pain that worsens with jaw motion. The pain can be accompanied by tinnitus and may radiate to the ear and periorbital region and down the mandible.
- On physical examination, muscles of mastication may be tender, tooth wear from bruxism can be present, and jaw movement may result in clicking or even locking that limits jaw opening.
- The diagnosis of TMJ disorders is primarily based on history and physical examination findings.

Treatment

- **Patient education and self-care measures:** Avoidance of triggers and consumption of a soft diet
- **Pharmacology:** NSAIDs and corticosteroid injections
- Dental splints if bruxism is suspected

MYOFASCIAL PAIN SYNDROME

Myofascial pain syndrome shares some clinical features with fibromyalgia. It is characterized as a regional pain disorder having trigger points within fascia and muscles.

History/PE

- Patients complain of a deep aching pain, often accompanied by a burning sensation and restricted active motion in the affected area.
- Physical examination reveals indurated regions known as trigger points. Palpating a trigger point reproduces pain in another location known as the “target zone.” Myofascial pain syndrome differs from fibromyalgia, as the latter does not have indurated trigger points and the tender points are located within tissues other than muscles.

Treatment

Multidisciplinary patient education, sleep hygiene, low-impact exercise, physical therapy, non-narcotic pain medications, antidepressants, gabapentin, and muscle relaxants.

SYSTEMIC SCLEROSIS

Also called scleroderma; characterized by chronic inflammation leading to progressive tissue fibrosis through excessive deposition of types I and III collagen. Commonly manifests as CREST syndrome (limited form, 80% of cases), but can also occur in a diffuse form (20% of cases) involving the skin and multiple organ systems. Risk factors include female sex and age between 35 and 50 years.

MNEMONIC

CREST syndrome—

Calcinosis
Raynaud phenomenon
Esophageal dysmotility
Sclerodactyly
Telangiectasias

History/PE

- Examination that may reveal symmetric thickening of the skin of the face and/or distal extremities
  - **Limited cutaneous:** Head, neck, distal upper extremities (earliest areas of involvement)
  - **Diffuse cutaneous:** Torso, abdomen, proximal upper extremity/shoulder
- **CREST syndrome:** Associated with limited cutaneous type
- **Diffuse form:** Leading to gastrointestinal (GI) dysmotility, pulmonary fibrosis, cor pulmonale, acute renal failure (scleroderma renal crisis), Raynaud phenomenon, and malignant hypertension
  - Scleroderma renal crisis is characterized by an abrupt onset of hypertension and acute renal failure in patients with scleroderma. Early recognition is crucial, as scleroderma renal crisis has a high mortality rate if not treated.

Diagnosis

- Diagnosis and categorization depend on constellation of symptoms.
- RF and ANA may be ⊕. Ninety-five percent of patients will have ⊕ ANA.
- Antiscleroderma (anti-Scl)-70/antitopoisomerase-I is highly specific (>99%) but only has ~20% to 45% sensitivity. These antibodies are associated with diffuse disease and poor prognosis.
- RF may also be ⊕.
- Anticentromere antibodies are specific for CREST syndrome (see Table 2.8-9). Severe disease may cause microangiopathic hemolytic anemia with schistocytes.

KEY FACT

Presence of anti-RNA polymerase III antibody in scleroderma is a risk factor for renal crisis.

Treatment

- Organ-based treatment that includes frequent monitoring for progressive damage and symptomatic support where necessary
- Corticosteroids for acute flares (but they increase the patient's risk for renal crisis); methotrexate for limited scleroderma
- Calcium channel blockers (dihydropyridine) such as amlodipine for Raynaud phenomenon
- Angiotensin-converting enzyme inhibitors for treatment of renal crisis

Complications

Mortality is most commonly caused by complications of ILD/pulmonary fibrosis, pulmonary hypertension, and resulting renal or cardiac disease.

SYSTEMIC LUPUS ERYTHEMATOSUS

A chronic multisystem autoimmune disorder related to antibody-mediated cellular attack and deposition of antigen-antibody complexes in any organ system, resulting in variable clinical manifestations and presentations. Black women are at highest risk. SLE usually affects women of childbearing age.

History/PE

Presents with nonspecific symptoms such as fever, anorexia, weight loss, and symmetric joint pain. Clinical heterogeneity and nonspecific symptoms present a diagnostic difficulty in many patients, making SLE a diagnosis of exclusion.

MNEMONIC

Criteria for SLE—

DOPAMINE RASH

Discoid rash
Oral ulcers
Photosensitivity
Arthritis (nondeforming)
Malar rash (see Fig. 2.8-13)
Immunologic criteria: anti-dsDNA, anti-Sm proteins, antiphospholipids
Neurologic symptoms (lupus cerebritis, seizures)
Elevated ESR
Renal disease
ANA ⊕
Serositis (pleural or pericardial effusion)
Hematologic abnormalities

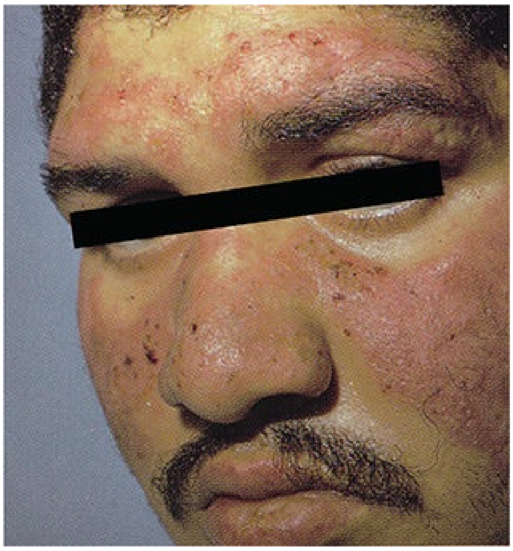


FIGURE 2.8-13. **Systemic lupus erythematosus (SLE).** The malar rash of SLE is red to purple with a continuous plaque extending across the bridge of the nose and to both cheeks. It typically spares the nasolabial folds. (Reproduced with permission from Bondi EE. *Dermatology: Diagnosis and Therapy*. Stamford, CT: Appleton & Lange; 1991.)

Diagnosis

- The mnemonic **DOPAMINE RASH** summarizes the criteria for diagnosing SLE, an adaptation of the American College of Rheumatology (ACR) criteria. Patients must have four of the criteria to consider a diagnosis of SLE (96% sensitive and specific).
- A ⊕ ANA is highly sensitive (present in 95%–99% of cases). If ⊕ ANA, the physician should test for other antibodies, mainly anti-dsDNA and anti-Sm. Both are highly specific but not as sensitive (see Table 2.8-9).
  - **Drug-induced SLE:** ⊕ antihistone antibodies are seen in 100% of cases but are nonspecific. Common medications include hydralazine, procainamide, and isoniazid.
  - **Neonatal SLE:** It is associated with ⊕ anti-Ro antibodies transmitted from mother to neonate. The presence of anti-Ro antibodies may cause heart block.
- The following may also be seen:
  - Low complement levels during acute flares
  - Antiphospholipid antibodies (antibodies to anticardiolipin, anti–β_2-glycoprotein, or lupus "anticoagulant"). All cause a hypercoagulable state and may cause thromboembolism and recurrent spontaneous abortion.
  - Raynaud phenomenon
  - Anemia, leukopenia, and/or thrombocytopenia
  - Proteinuria and/or casts

KEY FACT

The lupus anticoagulant (antiphospholipid antibodies) occurs in 5% to 10% of SLE cases. IgM or IgG binds proteins in a clinical assay test and prolongs partial thromboplastin time (PTT).

KEY FACT

Libman-**S**acks **En**docarditis: Noninfectious vegetations often seen on the mitral valve in association with SLE and antiphospholipid syndrome. Note ***L-S E***ndocarditis corresponds with S-L-E.

Treatment

- NSAIDs for mild joint symptoms.
- Corticosteroids for acute exacerbations. Be wary of Cushing syndrome and possible AVN from chronic use.
- Corticosteroids, hydroxychloroquine, cyclophosphamide, mycophenolate, and azathioprine for progressive or refractory cases. A few have specific uses:
  - Hydroxychloroquine: Can be used for isolated skin and joint involvement.
  - Cyclophosphamide or mycophenolate: Used for severe cases of lupus nephritis. The physician should be sure to get a renal biopsy for patients with nephritic symptoms.

Complications

Common causes of morbidity and mortality are important to know for SLE, including renal failure, cardiovascular disease, and infections.

KEY FACT

SLE can cause a false ⊕ Venereal Disease Research Laboratory (VDRL) test or rapid plasma reagin (RPR) test!

KEY FACT

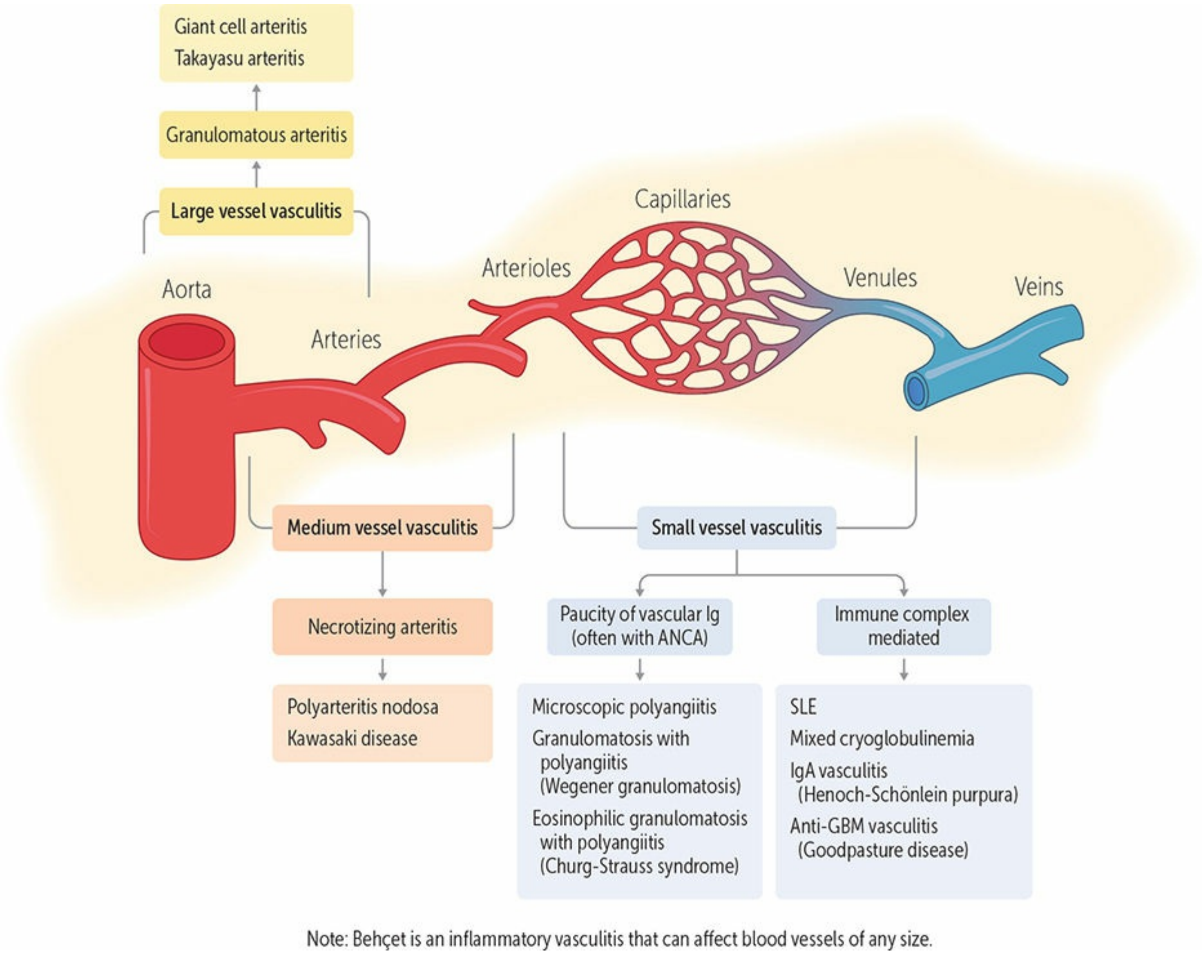
SLE and RA both affect the MCP and PIP joints; the difference is that in SLE, the joint disease is nondeforming and nonerosive, a pattern called Jaccoud arthropathy.

SERUM SICKNESS–LIKE REACTION

Self-limited fever, urticarial rash, arthralgia, lymphadenopathy, and proteinuria within 1 to 2 weeks of exposure to a β-lactam antibiotic (eg, penicillin, amoxicillin) or sulfa drug (eg, trimethoprim-sulfamethoxazole). Symptoms resolve upon discontinuation of the drug.

GIANT CELL ARTERITIS

Most common of the systemic vasculitides. Formerly called temporal arteritis. Caused by subacute granulomatous inflammation of the large vessels, including the aorta, external carotid (especially the temporal branch), and vertebral arteries (see Fig. 2.8-14). Risk factors include polymyalgia rheumatica (affects almost one half of patients), >50 years of age, and female sex.


Giant cell arteritis
Takayasu arteritis
Granulomatous arteritis
Large vessel vasculitis
Aorta
Arteries
Arterioles
Capillaries
Venules
Veins
Medium vessel vasculitis
Necrotizing arteritis
Polyarteritis nodosa
Kawasaki disease
Small vessel vasculitis
Paucity of vascular Ig (often with ANCA)
Immune complex mediated
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegener granulomatosis)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
SLE
Mixed cryoglobulinemia
IgA vasculitis (Henoch-Schönlein purpura)
Anti-GBM vasculitis (Goodpasture disease)

Note: Behçet is an inflammatory vasculitis that can affect blood vessels of any size.

FIGURE 2.8-14. **Classification of vasculitis according to vessel size.** (Reproduced with permission from USMLE-Rx.com.)

History/PE

- Presents with new headache (unilateral or bilateral), scalp pain, temporal tenderness, and jaw claudication
- Fever, permanent monocular blindness, transient monocular vision loss, aortic aneurysm, weight loss, and myalgias and/or arthralgias (especially of the shoulders and hips) also seen

Diagnosis

- **Best initial test:** ESR >50 mm/hr (influenced by age).
- **Most accurate test:** Temporal artery biopsy. The physician should look for thrombosis; necrosis of the media; and the presence of lymphocytes, plasma cells, and giant cells.

Treatment

- **Best initial treatment:** High-dose prednisone immediately to prevent ocular involvement (or involvement of the remaining eye after onset of monocular blindness). If suspected as contribution to vision loss, give pulse-dose steroids.
- A temporal artery biopsy to confirm diagnosis. However, do not delay treatment. Conduct a follow-up eye examination.

Complications

The most feared manifestation is blindness from anterior ischemic optic neuropathy (AION) secondary to occlusion of the posterior ciliary artery, a branch of the ophthalmic artery, which itself is a branch of the internal carotid artery. Central retinal artery (a branch of the internal carotid artery) occlusion is less common; however, if affected it may initially present as transient vision loss.

Q

A 55-year-old woman presents to the clinic with a chief complaint of “blindness.” She states that she experienced a temporary loss of vision in her left eye. She has also been experiencing new headaches and soreness in her jaw. Her vision exam is unremarkable. What diagnostic exam should be ordered?

TAKAYASU ARTERITIS

Large-vessel autoimmune vasculitis affecting the aorta and primary branches. Common in Asian females <40 years of age. Diagnosis made through clinical presentation and imaging. Classic symptoms include aortic claudication, differential blood pressure in both upper extremities, and the absence of palpable pulses (pulseless disease). ESR and CRP are often highly elevated. Imaging (magnetic resonance angiography [MRA] or computed tomography angiography [CTA]) will show narrowing of aorta or its primary branches. Treatment calls for oral high-dose steroids.

BEHçET SYNDROME

Autoimmune vasculitis common in males of Turkish or Middle Eastern descent. Characterized by recurrent, painful oral and genital ulcers and uveitis. Thrombosis is a common cause of morbidity. To prevent recurrence, patients should be treated with colchicine. Topical steroids can treat oral and genital ulcers, with ophthalmic steroids treating ocular involvement.

FIBROMYALGIA

A chronic musculoskeletal pain disorder that primarily affects young females and is characterized by soft tissue and axial skeletal pain in the absence of joint pain. Inflammation is notably absent (see Table 2.8-10). Fibromyalgia may be difficult to distinguish from myofascial pain (<11 painful areas).

TABLE 2.8-10. Fibromyalgia vs Polymyalgia Rheumatica

CHARACTERISTIC	FIBROMYALGIA	POLYMYALGIA RHEUMATICA
Age and sex	Females 30–50 years of age	Females >50 years of age
Location	Various	Shoulder and pelvic girdle
ESR	Normal	Markedly ↑ (>100 mm/hr)
CK	Normal	Normal
Muscle biopsy	Normal	Normal
Classic findings	Anxiety, stress, point tenderness, ⊖ workup	Temporal arteritis; response to steroids
Treatment	Antidepressants, NSAIDs, rest	Low-dose prednisone

- ***Hx/PE:*** Most common in females 30 to 50 years of age; associated with depression, anxiety, sleep disorders, irritable bowel syndrome (IBS), and cognitive disorders (“fibro fog”).
- ***Dx:*** Multiple painful areas over all four body quadrants and the axial skeleton for more than 3 months. The absence of any other pathology suggests a diagnosis of fibromyalgia.
- ***Tx:*** Initial nonpharmacologic approach, including multidisciplinary patient education regarding disease process, good sleep hygiene, low-impact exercise with psychotherapy, and physical therapy (stretching, heat, hydrotherapy). Next step: Pharmacologic options, including antidepressants (tricyclic antidepressant or serotonin-norepinephrine reuptake inhibitors), gabapentin, pregabalin, or muscle relaxants. Avoidance of narcotics.

A

Monocular amaurosis fugax is associated with giant cell (temporal) arteritis and may progress to complete vision loss. A temporal artery biopsy should be obtained.

POLYMYALGIA RHEUMATICA

An inflammatory rheumatic condition characterized by aching and stiffness in the shoulders, hips, and neck. Associated with temporal arteritis. Risk factors include female sex and >50 years of age (see Table 2.8-10).

History/PE

- Patient presents with pain and stiffness of the shoulder and pelvic girdle musculature with difficulty getting out of a chair or lifting arms above the head.
- Other symptoms include fever, malaise, and weight loss. Weakness is generally not appreciated on examination.

Diagnosis

An elevated ESR and/or CRP, normal creatine kinase (CK).

Treatment

Low-dose prednisone (10–20 mg/day).

UPPER EXTREMITY

ADHESIVE CAPSULITIS

Adhesive capsulitis ("frozen shoulder") is a pathology of the glenohumeral joint in which the shoulder loses its normal ROM. This condition can be either idiopathic or result from several predisposing conditions such as shoulder injury (eg, rotator cuff tear, humeral fracture, or surgery), subacromial bursitis, diabetes mellitus, hypothyroidism, Dupuytren contracture, or paralytic stroke.

History/PE

- Adhesive capsulitis presents in middle-aged and older individuals.
- Patients complain of gradual onset of poorly localized, nagging shoulder pain that is worse at night.
- The pain is accompanied by a significant reduction in both active and passive shoulder ROM. Patients may particularly complain of their inability to reach overhead or difficulty in back scratching or putting on a coat.

Diagnosis

Clinical diagnosis. Based on demonstration of both active and passive shoulder mobility reduction in multiple planes. Imaging is not typically required unless to rule out another shoulder pathology.

Treatment

- Most cases are managed with ROM exercises and physical therapy.
- Cases having limited success with ROM exercises may be treated with corticosteroid injections, as well as arthroscopic distention and surgical release and NSAIDs.

ROTATOR CUFF INJURIES

Rotator cuff pathology is a common cause of pain in older adults, and it typically relates to impingement, glenohumeral OA, or an acute traumatic event. The supraspinatus is most commonly torn, but the subscapularis, infraspinatus, or teres minor may also be involved. Sports that require overhand motion (eg, baseball, swimming) may cause tears in young adults. Impingement or tendinopathy may precede a full rotator cuff tear.

KEY FACT

Tendinitis is a slight misnomer, as a classic cellular inflammatory response is absent or minimal in cases of overuse tendinopathy. Tendinosis is a more appropriate term referring to chronic tendinopathy without cellular inflammation (eg, rotator cuff tendinopathy).

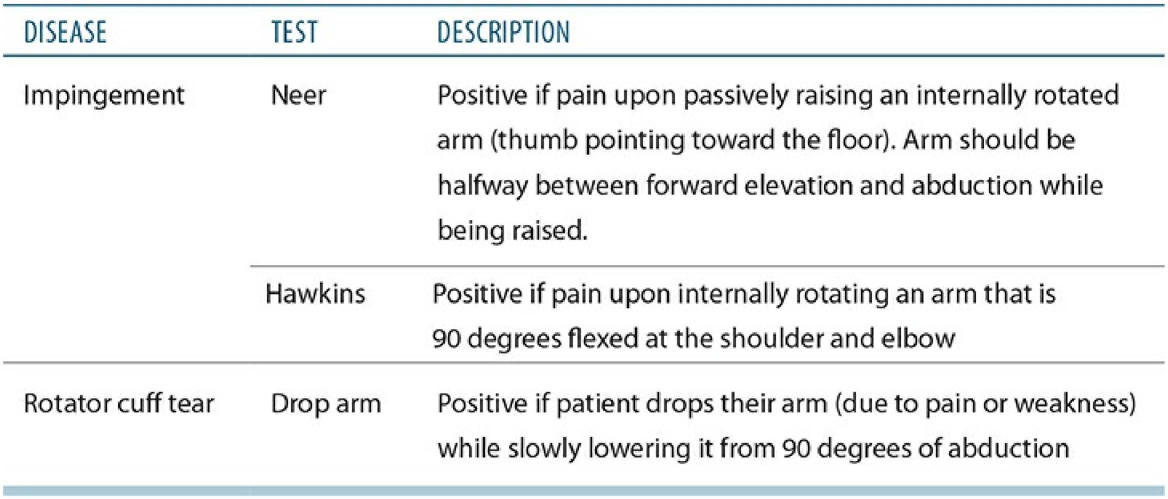
KEY FACT

Rotator cuff tears can be acute or chronic. Chronic tears cause gradual pain and typically are seen in older adults. Impingement syndrome involves pain caused by compression of soft tissue structures, and it may have a more insidious onset.

History/PE

- **Impingement:** Normal ROM but painful abduction and external rotation. Neer sign and Hawkins test for impingement may be positive (see Table 2.8-11).

TABLE 2.8-11. **Physical Examination Maneuvers for Shoulder Pathology**



DISEASE	TEST	DESCRIPTION
Impingement	Neer	Positive if pain upon passively raising an internally rotated arm (thumb pointing toward the floor). Arm should be halfway between forward elevation and abduction while being raised.
	Hawkins	Positive if pain upon internally rotating an arm that is 90 degrees flexed at the shoulder and elbow
Rotator cuff tear	Drop arm	Positive if patient drops their arm (due to pain or weakness) while slowly lowering it from 90 degrees of abduction

- **Tear:** Painful and weak abduction and external rotation. Drop arm sign may be positive if supraspinatus is torn. Risk factors include trauma, dislocation, and age >40 years.

Diagnosis

- **Impingement:** X-ray
- **Tear:** If suspicion high (eg, preceding trauma, weakness, and ⊕ drop arm), MRI best next test

Treatment

Many patients improve with conservative management (eg, physical therapy). The physician may consider repair if patient is refractory or fails physical therapy.

COMPARTMENT SYNDROME

↑ pressure within a confined space that compromises nerve, muscle, and soft tissue perfusion. Occurs most commonly in the anterior compartment of the lower leg and in forearm secondary to trauma to the affected limb (fracture or muscle injury). Compartment syndrome can also occur due to nontraumatic causes such as (1) thrombosis leading to ischemia-reperfusion injury or (2) prolonged limb compression (eg, in a patient who overuses alcohol or drugs).

History/PE

- Symptoms develop acutely over several hours. Patient presents with **P**ain **O**ut **O**f

Proportion **(POOP)** to physical findings; **P**ain with passive motion of the fingers and toes; and **P**aresthesias, **P**allor, **P**oikilothermia, **P**ulselessness, and **P**aralysis (the **six Ps**).

- Paralysis and pulselessness occur as late signs of compartment syndrome.

KEY FACT

Volkmann contracture of the wrist and fingers is caused by compartment syndrome, which is associated with supracondylar humerus fractures. These fractures may affect the brachial artery and radial nerve. Ischemia results in fibrosis of dead muscle.

KEY FACT

Timeline of the six Ps in compartment syndrome:
Early (nerve dysfunction) — Pain out of proportion, paresthesia
Late (vascular insufficiency) — Pallor, poikilothermia → Paralysis, pulselessness

Diagnosis

Based on history, serial examinations, and elevated compartment pressure >30 mm Hg (although not necessary). The physician should calculate delta pressure (diastolic pressure – compartment pressure); the diagnosis is ⊕ if delta pressure ≤30 mm Hg.

Treatment

- Emergent fasciotomy to ↓ pressures and ↑ tissue perfusion.
- Time to fasciotomy is one of the most important prognostic factors.
- If <6 hours from symptom onset, limb recovery approaches ~100%.
- If >6 hours from symptom onset, residual nerve dysfunction, muscle death, and need for amputation likelihood increase.

KEY FACT

Open fractures are an orthopedic emergency. Closed tibia and forearm fractures have higher rates of compartment syndrome. Patients should be taken to the operating room within 8 to 24 hours for irrigation and debridement followed by fracture repair. The physician should reduce infection risk with antibiotics and tetanus prophylaxis.

RHABDOMYOLYSIS

Caused by muscle necrosis and subsequent release of byproducts into systemic circulation. Hallmark finding is elevated CK. Etiologies include direct muscle damage (trauma, compression, compartment syndrome), extreme exertion (power lifters, marathon runners), toxins, or a syndrome such as malignant hyperthermia.

History/PE

- Commonly presents with muscle pain and weakness; however, can be asymptomatic
- Dark or “bloody” urine secondary to myoglobinuria

Diagnosis

- ↑↑ serum CK, usually >1500 U/L or five times the upper limit of normal
- Urinalysis ⊕ for myoglobin, minimal RBCs, possibility of acute kidney injury (AKI)
- Hyperkalemia, hyperphosphatemia

Treatment

- IV fluid resuscitation and correction of electrolyte abnormalities
- Treatment of etiology if applicable (compartment syndrome, malignant hyperthermia)

Complications

AKI occurs in 15% to 50% with rhabdomyolysis due to volume depletion and direct nephron injury from myoglobin acting as a direct toxin.

Q

A 37-year-old man is seen after a motorcycle accident. He complains of intense leg pain, tingling in his foot, and inability to move his toes. A physical examination reveals pain with passive motion of his toes and palpable dorsalis pedis pulses. An x-ray film confirms a tibial fracture. What is the best treatment?

CARPAL TUNNEL SYNDROME

Entrapment of the median nerve at the wrist caused by ↓ size or space of the carpal tunnel, leading to paresthesia, pain, and occasionally paralysis. Can be precipitated by overuse of wrist flexors; associated with pregnancy, diabetes mellitus, hypothyroidism, acromegaly, RA, and amyloidosis

KEY FACT

Pronator syndrome (PS) is due to compression of the median nerve at the elbow. Symptoms include paresthesia in a similar distribution to carpal tunnel syndrome. Patients also have fewer night symptoms and may have a positive Tinel sign at the proximal, anterior forearm. One risk factor: Hypertrophic forearm muscles.

KEY FACT

Sensory loss in carpal tunnel syndrome is a late finding that spares the thenar eminence, as this area is supplied by the palmar sensory cutaneous nerve, which arises proximal to the carpal tunnel and passes over it.

History/PE

- Difficulty with daily activities such as typing, turning doorknobs, opening a bottle cap, and driving
- Presents with aching over the thenar area of the hand and proximal forearm
- Paresthesia or numbness seen in a median nerve distribution (first three and a half digits)

- Symptoms that worsen at night and awaken patient from sleep
- Examination that shows thenar eminence atrophy (if disease is long-standing)
- Phalen maneuver and Tinel test ⊕ (see Fig. 2.8-15). Durkan test (carpal compression test) is another provocative method to diagnose carpal tunnel syndrome.

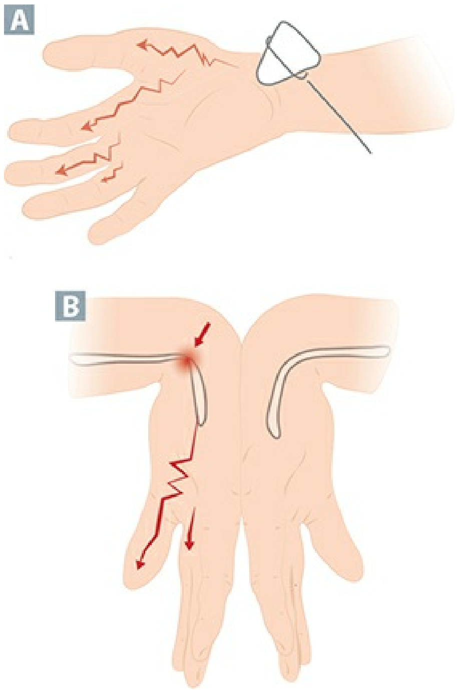


FIGURE 2.8-15. **Carpal tunnel syndrome. (A)** The Tinel test is performed by tapping the volar surface of the wrist over the median nerve. **(B)** The Phalen maneuver is performed by compressing the opposing dorsal surfaces of the hand with the wrists flexed together as shown. This causes tingling over the median nerve distribution. (Modified with permission from USMLE-Rx.com.)

Diagnosis

- Usually a clinical diagnosis from symptoms and signs
- Electrodiagnostic tests: Nerve conduction studies and electromyography

Treatment

- **Best initial treatment:** Splinting the wrist in a neutral position at night and during the day if possible
- **Medical treatment:** Corticosteroid injection of the carpal canal and NSAIDs
- **Most definitive treatment:** Surgical decompression of the tunnel, a widely accepted treatment, particularly for fixed sensory loss, thenar weakness, or intolerable symptoms with no improvement after splinting and/or glucocorticoids

Complications

Permanent loss of sensation, hand strength, and fine motor skills.

GANGLION CYST

Fluid-filled cyst arising from tendon sheaths, ligaments, or joint connective tissue. Most commonly arises in the dorsum of the wrist (see Fig. 2.8-16)

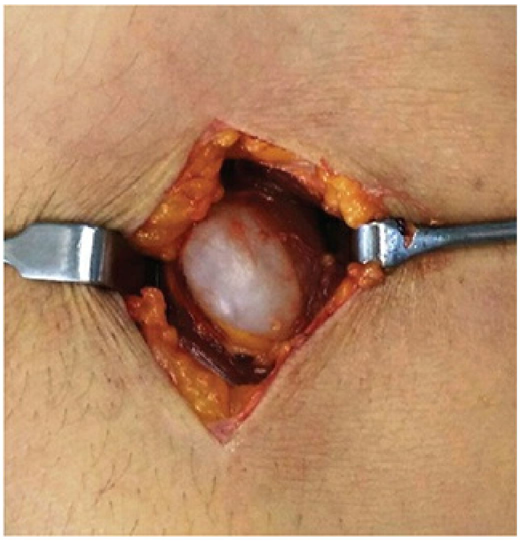


FIGURE 2.8-16. **Ganglion cyst.** (Reproduced with permission from Vaishya R, Kapoor C, Agarwal AK, Vijay V. A rare presentation of ganglion cyst of the elbow. *Cureus*. 2016 Jul 1;8(7):e665. doi: 10.7759/cureus.665.)

History/PE

- A ganglion cyst commonly presents with a slowly growing mass overlying the joint and causing wrist pain.
- The mass will be rubbery, round, and firm. It will be relatively immobile due to association with joint connective tissue.

Diagnosis

Transillumination will show a fluid-filled structure, and it can guide diagnosis. Ultrasound may differentiate a simple from a multiloculated cyst or a solid structure (eg, lipoma, tumor, nodule).

A

The best treatment is immediate fasciotomy for compartment syndrome (within 6 hours to prevent muscle necrosis) followed by fracture stabilization. Remember that nonpalpable pulses are a late finding.

Treatment

- Observation. Up to 50% of ganglion cysts spontaneously regress.
- Surgical excision for ganglion cysts that do not regress, are symptomatic, or have features concerning for malignancy. The recurrence rate is ~10%.

DUPUYTREN CONTRACTURE

Due to disorder in fibroblastic proliferation and deposition of collagen in the palmar fascia of the hand with progressive fibrosis. Dupuytren contracture often presents after the fifth decade of life, predominantly in White males.

History/PE

- Often begins as a painless nodule in the palm with progressive thickening and development of palmar cords

- Eventually advances to a permanent contracture and flexion of the digits with inability to extend
- Mostly affects ulnar aspect of hands, with MCP and PIP joints of the fourth and fifth digits most commonly affected

Diagnosis

- Characteristic palmar nodules or cords, depending on clinical stage
- Physical examination demonstrating inability to extend the fingers or joints

Treatment

- Surgical correction with fasciotomy (transection) or fasciectomy (excision) of cords
- Percutaneous needle aponeurotomy less invasive but less effective in relieving contracture

Complications

High recurrence rate, even after surgical correction.

AVASCULAR NECROSIS

AVN, also known as osteonecrosis or ischemic necrosis, is caused by disruption of proximal blood supply, leading to death of bone (see Fig. 2.8-17). Two commonly tested concepts are AVN of the scaphoid bone (after a fall onto an outstretched hand [FOOSH]) and AVN of the femoral head (associated with a variety of conditions).

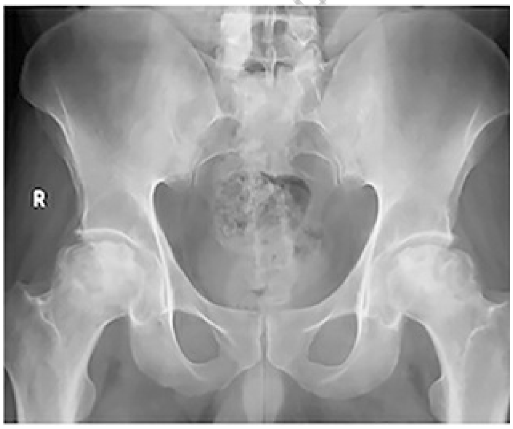


FIGURE 2.8-17. **Femoral head AVN.** (Reproduced with permission from Bilge O, Doral MN, Yel M, Karalezli N, Miniaci A. Treatment of osteonecrosis of the femoral head with focal anatomic-resurfacing implantation (HemiCAP): Preliminary results of an alternative option. *J Orthop Surg Res.* 2015;10:56. Published 2015 Apr 28. doi:10.1186/s13018-015-0199-3.)

History/PE

- **Scaphoid necrosis:** Pain at the anatomic snuff box after a FOOSH
- **Femoral head necrosis:** Dull or sharp pain in the affected hip
- **Children:** Idiopathic AVN (Legg-Calve-Perthes disease) or slipped capital femoral epiphysis
- Sickle cell disease, prolonged glucocorticoid or bisphosphonate use, femoral fracture

Diagnosis

- X-ray of the affected wrist or hip. MRI is gold standard for those with negative x-ray and high suspicion for AVN.

- In scaphoid fractures, x-rays possibly negative for 2 to 6 weeks after a fall. It is important to get delayed follow-up imaging to rule out necrosis or displacement.

Treatment

- **Scaphoid AVN:** Wrist splints after fall; surgical referral for displaced fractures or those with neurovascular compromise
- **Femoral head AVN:** Total hip replacement

RAYNAUD PHENOMENON

Abnormal vasoconstriction of peripheral arteries in response to cold, leading to characteristic progression of digit color changes reflecting pathologic process.

- **Ischemia:** Vasospasm of artery causing occlusion and pallor → pale “white” digits
- **Cyanosis:** Dilation of capillaries and filling of deoxygenated blood → “blue” digits
- **Rubor:** Resolution of arterial vasospasm and reperfusion → “red” digits

May be primary or associated with other autoimmune conditions. Test for ANA and RF to lead to diagnosis. First-line treatment is general avoidance of triggers. Pharmacologic treatment calls for calcium channel blockers (eg, amlodipine, nifedipine).

KEY FACT

Raynaud phenomenon may be triggered by cold temperatures and stress. Keeping the body’s core warm is essential. It can be treated with calcium channel blockers (CCBs) such as nifedipine or amlodipine.

HAND INFECTIONS AND BITE WOUNDS

Acute hand infections and bites should be promptly evaluated and treated. Both animal and human bites should be empirically treated. A “fight bite” is a laceration from striking another’s mouth and should be carefully examined due to high mouth colonization and possibility for progression to a septic joint. Surgical debridement should be done by an orthopedic or hand specialist.

History/PE

- Presents with hand pain and erythema, often with loss of ROM due to edema
- **Alarm signs:** Crepitus, indicating possible necrotizing infection, and skin discoloration, indicating necrosis or ischemia

Diagnosis

- **Laboratory studies:** Leukocytosis may assess severity of infection and help monitor progression. Cultures of wounds can help guide antibiotic treatment.
- **Imaging:** Plain radiographs should be first-line to evaluate bones for possible fracture or osteomyelitis, foreign bodies, affected joints, or subcutaneous gas.

Treatment

- Broad-spectrum antibiotics should be first-line until cultures can guide therapy.
- Treatment should be based on source of bite. Dog and cats—*Pasteurella*, *Staphylococcus*,

Streptococcus. Human—*Eikenella*, group A *Streptococcus*.

- Necrotizing infections and severe infections require surgical debridement and source control to prevent permanent compromise.
- Septic arthritis requires joint aspiration and urgent surgical debridement.

Complications

Progression of infection can require emergent surgical intervention, and without proper treatment can lead to loss of digits, limb, or permanent disfigurement and disability.

LOWER EXTREMITY

OSTEOCHONDRITIS DISSECANS

Osteochondritis dissecans (OCD) often presents in adolescent children in which a part of the subchondral bone detaches from the underlying bone (see Fig. 2.8-18). OCD has a propensity to affect boys. It results from repeated trauma in highly active children. The most common joints involved include the knee, elbow, and ankle (often with a history of ankle inversion).

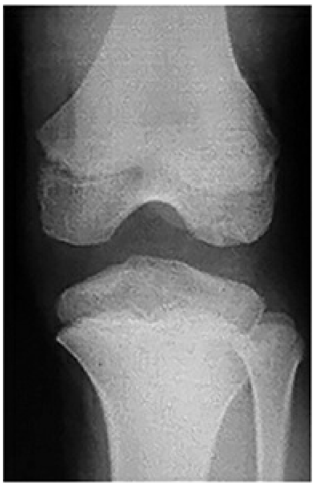


FIGURE 2.8-18. **Osteochondritis dissecans.** Subchondral bone detaches from the underlying bone. (Reproduced with permission from Kanto R, Nakayama H, Iseki T, Yoshiya S. Juvenile osteochondritis dissecans in the lateral femoral condyle requiring osteochondral autograft as a revision procedure: A case report. *J Med Case Rep.* 2016;10:3 doi:10.1186/s13256-015-0795-1.)

- ***Hx:*** Patients complain of dull, poorly localized joint pain that worsens with activity. Accompanying swelling, stiffness, crepitus, and tenderness may be present. In advanced stages of the disease, patients can have an antalgic gait (patients rotate the affected limb laterally to reduce pain from weight-bearing) and complain of a catching and locking sensation.
- ***Dx:*** Based on visualization of subchondral bone fragment on plain radiograph. In case of high suspicion and normal radiograph, an MRI can be obtained.
- ***Tx:*** Rest, physical therapy, and surgery (in severe disease).

BURSITIS

Inflammation of the joint bursa by repetitive use, trauma, infection, systemic inflammatory disease (eg, autoimmune disease), or crystalline disorders (eg, gout). Common sites of bursitis include subacromial, olecranon, trochanteric, popliteal fossa (Baker cyst), prepatellar (housemaid's knee), and infrapatellar bursae.

- ***Hx/PE:*** Presents as pain, tenderness, swelling, and reduction on active ROM but with limited impact on passive ROM. Presence of abrasion, overlying cellulitis, or puncture wound/history of bursal injection with accompanying fever and chills suggests a septic etiology (often due to *S aureus*).
- ***Dx:*** Based on history and PE. In case of suspected septic or crystalline etiology, aspiration should be performed.
- ***Tx:*** Activity modification and NSAIDs for nonseptic cases. In case of septic etiology, systemic antibiotics are required, with surgical debridement in selected cases.

PES ANSERINUS PAIN SYNDROME

Also called anserine bursitis. Common in young adults active in sports, overweight middle-aged females, and older adults with OA. Presents with localized pain at the anteromedial tibia at the insertion of the pes anserinus (just below the joint line) that is aggravated by overuse, obesity, knee OA, and pressure from the opposite knee while lying on the side. Pain typically develops over weeks and worsens overnight. Valgus stress test will not aggravate the pain, and x-rays will also be normal. Treatment includes NSAIDs and strengthening of quadricep muscles.

Q

A 23-year-old man presents to the emergency department with a swollen and erythematous right hand following an altercation at a bar a few days ago. The dorsum of the hand shows abrasions, and x-ray films reveal a fracture of the fifth metacarpal. What is the next step in management?

PATELLOFEMORAL PAIN SYNDROME

Anterior knee pain caused by overuse. Common in females, runners, cyclists, and athletes. Pain can be reproduced with knee extension or using stairs. Treatment calls for activity modification (often rest) and NSAIDs.

History/PE

Presents with localized tenderness, ↓ ROM, edema, and erythema; possible history of trauma or inflammatory disease. Pain is reproducible with squatting, and it worsens with ascending or descending stairs. Diagnosis can occur with patellar tendonitis (localized pain directly beneath patella).

KEY FACT

Infection of the superficial bursae occurs after trauma to the skin. Infection of deep bursae is often iatrogenic following injections or aspirations.

Diagnosis

- Mainly a clinical diagnosis based on symptoms and physical exam findings.

- Needle aspiration indicated if septic bursitis is suspected. No labs or imaging is needed.

Treatment

- **Best initial treatment:** Rest, heat and ice, elevation, and NSAIDs. Patient should increase quadriceps strength with physical therapy.
- An intrabursal corticosteroid injection can be considered, but it is contraindicated if septic bursitis is suspected.
- Septic bursitis should be treated with 7 to 10 days of antibiotics.

KEY FACT

In a child with gout and inexplicable injuries, consider Lesch-Nyhan syndrome (hypoxanthine-guanine phosphoribosyltransferase [HGPRT] deficiency).

MORTON NEUROMA

Neuropathic degeneration of nerves (most commonly between the third and fourth toes) that causes numbness, pain, and paresthesia. Often associated with a “clicking sensation” when palpating this joint space. Morton neuroma occurs in runners, and symptoms worsen when metatarsals are squeezed together (eg, from wearing high-heeled shoes or walking on hard surfaces). Treatment requires padded shoe inserts to decrease pressure on metatarsal heads or surgical removal.

GOUT

Recurrent attacks of acute monoarticular arthritis resulting from intra-articular deposition of monosodium urate crystals caused by disorders of urate metabolism (↑ production or ↓ excretion). Risk factors include male sex, obesity, postmenopausal status in women, and binge drinking.

KEY FACT

Gout crystals appear ye**LL**ow when para**LL**el to the condenser.

A

If skin is broken in a boxer’s fracture, assume infection by human oral pathogens and treat with surgical irrigation, debridement, and IV antibiotics to cover *Eikenella*.

History/PE

- Presents with sudden onset of excruciating joint pain. Gout is associated with erythema, warmth, swelling, and decreased ROM. Fever and mild leukocytosis can be present.
- Eighty percent of cases are monoarticular. Gout most commonly affects the first metatarsophalangeal (MTP) joint (podagra) and the midfoot, knees, ankles, and wrists; the hips and shoulders are generally spared.
- Tophi (urate crystal deposits in soft tissue) can be seen with chronic disease and are

associated with tissue destruction (see Fig. 2.8-19). Tophi are virtually pathognomonic for gout and are painless and nontender. They can ulcerate and discharge a chalky white substance.

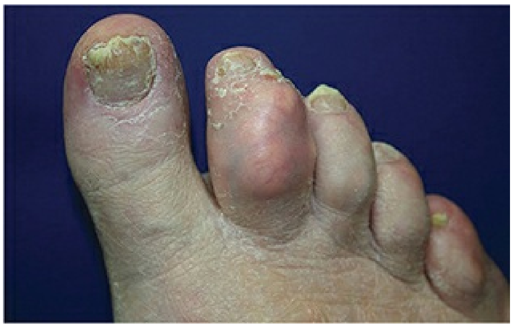


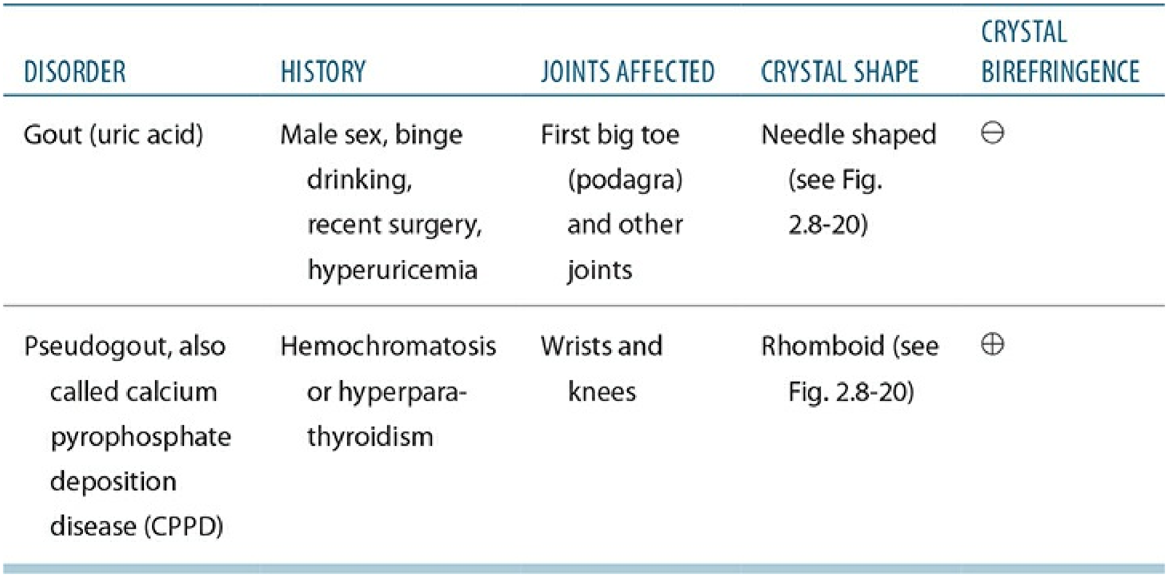
FIGURE 2.8-19. **Tophaceous gout.** Note the slowly enlarging nodule of the right second toe in a 55-year-old man who is hypertensive, takes hydrochlorothiazide, and overuses alcohol. (Reproduced with permission from USMLE-Rx.com.)

- Uric acid kidney stones are seen with chronic disease.

Diagnosis

- Diagnosis requires joint synovial fluid aspiration because septic arthritis can present similarly. Aspirate shows needle-shaped, negatively birefringent crystals (vs pseudogout; see Table 2.8-12).

TABLE 2.8-12. **Gout vs Pseudogout**



DISORDER	HISTORY	JOINTS AFFECTED	CRYSTAL SHAPE	CRYSTAL BIREFRINGENCE
Gout (uric acid)	Male sex, binge drinking, recent surgery, hyperuricemia	First big toe (podagra) and other joints	Needle shaped (see Fig. 2.8-20)	⊖
Pseudogout, also called calcium pyrophosphate deposition disease (CPPD)	Hemochromatosis or hyperparathyroidism	Wrists and knees	Rhomboid (see Fig. 2.8-20)	⊕

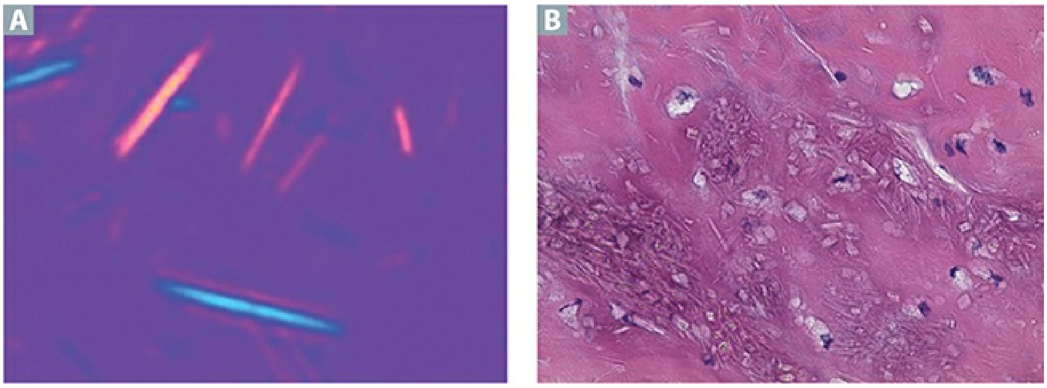


FIGURE 2.8-20. **Gout and pseudogout crystals.** Gout **(A)** has negatively birefringent needle-shaped crystals, but pseudogout **(B)** has rhomboid crystals under light microscopy. (Image A reproduced with permission from Manhas A, Kelkar P, Keen J, et al. Recurrent craniocervical pseudogout: indications for surgical resection, surveillance imaging, and craniocervical fixation. *Cureus*, 8(2): e511. doi:10.7759/cureus.511. Image B adapted with permission from Zhang Y, Lee SY, Zhang Y, et al. Wide-field imaging of birefringent synovial fluid crystals using lens-free polarized microscopy for gout diagnosis. *Sci Rep*, 2016;6:28793. doi:10.1038/srep28793.)

- Lab tests and imaging:
    - Serum uric acid is usually elevated (≥7.5 mg/dL), but patients may have normal or even decreased levels during an acute attack of gout. ESR and CRP are typically elevated, and joint fluid aspiration and analysis are required to clarify the diagnosis.
    - X-rays may show punched-out erosions with overhanging cortical bone ("rat-bite" erosions, see Fig. 2.8-21) that are seen in advanced gout.

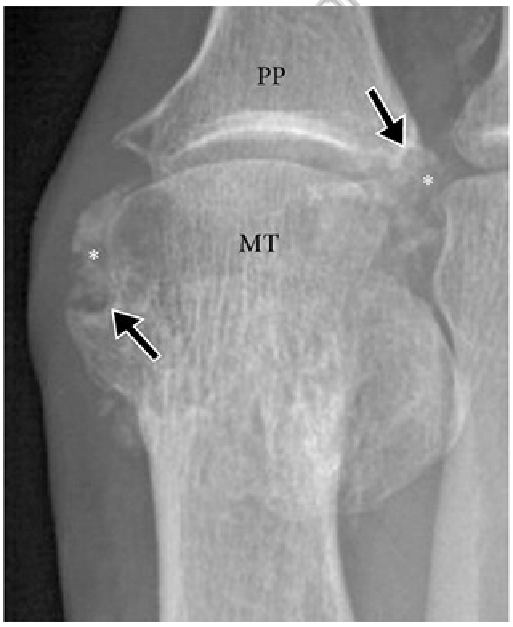


FIGURE 2.8-21. **Rat-bite lesions.** Punched-out erosions with overhanging cortical bone, seen in patients with gout. (Reproduced with permission from Girish G, Melville DM, Kaeley GS, et al. Imaging appearances in gout. *Arthritis.* 2013;2013:673401. doi:10.1155/2013/673401.)

KEY FACT

Causes of hyperuricemia:

- ↑ cell turnover (hemolysis, blast crisis, tumor lysis, myelodysplasia, psoriasis)
- Drugs: Cyclosporine, diuretics, low-dose salicylates
- Physiologic states: Dehydration, starvation, obesity

- Disease: DI, HGPRT deficiency, G6P deficiency
- Diet (eg, ↑ red meat, alcohol)
- Diuretics
- Lead poisoning
- Lesch-Nyhan syndrome
- Salicylates (low dose)

Q

A 49-year-old man presents with a painful, swollen big toe after a night of heavy drinking. How does alcohol affect uric acid metabolism?

Treatment

- Acute attacks:
  - High-dose NSAIDs (eg, indomethacin) are first-line. NSAIDs should be avoided in cases of congestive heart failure (CHF), chronic kidney disease (CKD), peptic ulcer disease, and for anticoagulated patients. Colchicine may also be used; it is most effective when used within 24 hours of attack onset.
  - Steroids are used when NSAIDs are ineffective or contraindicated (eg, renal insufficiency).
  - Intra-articular steroid injection is preferable if only one or two joints are involved. Otherwise, systemic steroids should be used.
- Maintenance therapy is indicated in case of two or more attacks annually, presence of tophi, or structural joint damage**.** Maintenance medications include:
  - Xanthine-oxidase inhibitors: Allopurinol and febuxostat. Can ↑ incidence of urate nephropathy
  - Uricosuric agents: Probenecid. Contraindicated in patients with tophi, nephrolithiasis, or CKD
- Weight loss and avoidance of triggers (eg, binge drinking, red meat) will prevent recurrent attacks in many patients.

KEY FACT

Allopurinol and febuxostat are both xanthine oxidase inhibitors. Allopurinol and febuxostat decrease metabolism of azathioprine or 6-mercaptopurine, leading to profound toxicities, and they should be avoided in patients who are on azathioprine or mercaptopurine (6-MP).

PSEUDOGOUT

Pseudogout is acute synovitis presenting similarly to gout attacks. Flares are common in a setting of recent surgery or medical illness. It is a disease of older adults, characterized by calcium pyrophosphate crystal deposition into the joint space. Peripheral joints are most commonly involved, classically the knee joint. Risk factors include hemochromatosis, hypothyroidism, and hypercalcemia.

KEY FACT

Colchicine inhibits neutrophil chemotaxis and is most effective in pseudogout when used within 24 hours of flare onset. However, it can cause diarrhea, neuromyopathy, and bone marrow suppression (neutropenia).

- ***Hx/PE:*** Same as gout (see previous section).
- ***Dx:*** Based on joint aspiration showing rhomboid-shaped birefringent crystals. Imaging classically reveals chondrocalcinosis (see Fig. 2.8-22).

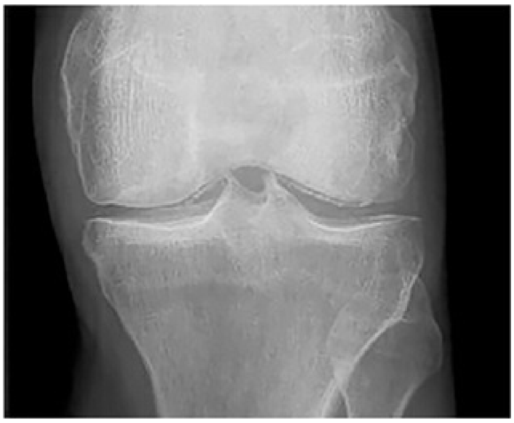


FIGURE 2.8-22. **Chondrocalcinosis.** Punctate and linear lesions that correlate with the deposition of calcium-containing crystals in articular cartilage. (Reproduced with permission from Hahn M, Raithel M, Hagel A, Biermann T, Manger B. Chronic calcium pyrophosphate crystal inflammatory arthritis induced by extreme hypomagnesemia in short bowel syndrome. *BMC Gastroenterol.* 2012;12:129. Published 2012 Sep 22. doi:10.1186/1471-230X-12-129.)

- ***Tx:*** Intra-articular steroids, NSAIDs, and colchicine.

A

Alcohol is a source of purines, which are metabolized into uric acid, increasing serum concentrations and predisposing patients to gout flares.

TRUNK

LOW BACK PAIN

Low back pain (LBP) is the second-leading symptom-related cause for office visits in the United States. Although often self-limited, it can also be a sign of more severe disease, including infection, malignancy, or abdominal aortic aneurysm (AAA). Routine imaging studies are not indicated in the majority of patients with acute LBP unless alarming symptoms are present.

KEY FACT

Most LBP is mechanical, so bed rest is contraindicated.

Red Flag Symptoms

Patient histories involving back pain that would warrant further imaging include:

- Constitutional symptoms (eg, fever, chills, night sweats)
- Sensory or motor deficits (eg, paresthesia or urine retention)
- Suspicion of infection (eg, immunosuppressive drugs, recent spinal procedure, endocarditis)
- Risk factors for compression fracture (eg, glucocorticoid use, older age, osteoporosis)
- History of drug abuse or malignancy

KEY FACT

Red flags for LBP include >50 years of age, >6 weeks of pain, previous cancer history, severe pain, constitutional symptoms, neurologic deficits, and loss of anal sphincter tone.

HERNIATED DISK

Causes include degenerative changes, trauma, or neck/back strain or sprain. A herniated disk most commonly occurs (95%) in the lumbar region, especially at L5–S1 (most common site) and L4–L5 (second most common site).

History/PE

- Presents with sudden onset of severe, electricity-like LBP, usually preceded by several months of aching, “diskogenic” pain
- Common among middle-aged and older males
- Exacerbated by ↑ intra-abdominal pressure (eg, coughing, sneezing) or Valsalva (eg, coughing)
- Associated with sciatica, paresthesia, muscle weakness, atrophy, contractions, or spasms
- A contralateral (crossed) straight-leg raise ↑ pain (highly specific but not sensitive)
- Large midline herniations can cause cauda equina syndrome

Diagnosis

- Diagnosed with a ⊕ passive straight-leg raise with increased pain (sensitive, not specific).
- **Imaging:** MRI (see Fig. 2.8-23) is the preferred test. It is necessary for cauda equina syndrome or for a severe or rapidly progressing neurologic deficit.

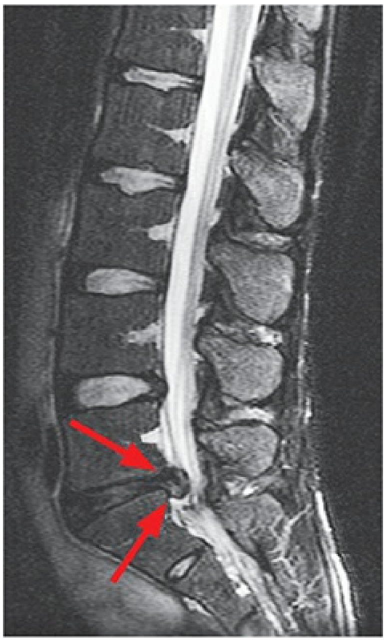


FIGURE 2.8-23. **Disk herniation.** Sagittal T2-weighted MRI of the lumbar spine shows posterior herniation of the L5-S1 disk. (Reproduced with permission from Fauci AS et al. *Harrison's Principles of Internal Medicine,* 17th ed. New York, NY: McGraw-Hill; 2008.)

- **Additional tests:** ESR and plain x-ray if other causes of back pain are suspected (eg, infection, trauma, compression fracture).

KEY FACT

Bowel or bladder dysfunction (urinary overflow incontinence), impotence, and saddle-area anesthesia are consistent with cauda equina syndrome, a surgical emergency.

Treatment

- **Best initial treatments:** NSAIDs in scheduled doses, physical therapy, and local heat. The physician should not prescribe bed rest; continuation of regular activities is preferred.
- **Epidural steroid injection or nerve block:** Patients who do not respond to initial treatment.
- **Most definitive treatment:** Surgery—only in focal neurologic deficits, cauda equina syndrome, and in cases of persistent pain for at least 6 weeks.

SPINAL STENOSIS

Narrowing of the lumbar or cervical spinal canal, leading to compression of the nerve roots and spinal cord. Most commonly caused by degenerative joint disease; typically occurs in middle-aged or older adult patients

History/PE

- Spinal stenosis presents with neck pain, back pain that radiates to the arms or the buttocks and legs bilaterally, and leg numbness/weakness.
- In lumbar stenosis, leg cramping is worse with standing and with walking downhill.
- In lumbar stenosis, symptoms improve with flexion at the hips and bending forward,

which relieves pressure on the nerves, aka, the “shopping cart sign.”

KEY FACT

Neurogenic claudication or pseudoclaudication is an important feature of lumbar spinal stenosis and is characterized by worsening symptoms with walking and relief with sitting or lying down.

Diagnosis

MRI is the main imaging modality to use.

Treatment

- **Mild to moderate:** Treatments include NSAIDs, weight loss, and abdominal muscle strengthening.
- **Advanced:** Epidural corticosteroid injections can provide relief.
- **Refractory:** Surgical laminectomy is needed in 75% of patients with refractory symptoms. Table 2.8-13 outlines the motor, reflex, and sensory deficits with which LBP is associated.

TABLE 2.8-13. Motor, Reflex, and Sensory Deficits in Back Pain

	ASSOCIATED DEFICIT		
NERVE ROOT	MOTOR	REFLEX	SENSORY
L2–L4	Hip flexion (psoas), knee extension (quadriceps), and foot dorsiflexion (tibialis anterior)	Patellar	Anterior thigh and medial aspect of the lower leg
L5	Big toe dorsiflexion (extensor hallucis longus), foot eversion (peroneus muscles)	None	Dorsum of the foot and lateral aspect of the lower leg
S1	Plantarflexion (gastrocnemius/soleus), hip extension (gluteus maximus)	Achilles	Lateral aspects of the foot and little toe
S2–S4	Incontinence and sexual dysfunction	Anocutaneous	Posterior, medial thigh, and perianal

SPONDYLOLISTHESIS AND SPONDYLOSIS

Spondylosis is a common cause of LBP in preadolescent children and athletes with repetitive back extension and rotation (divers, gymnasts). It represents a bilateral fracture of the posterior arch, whereas spondylolisthesis involves the anterior displacement of vertebrae (usually L5, S1) due to a defect in the posterior arch.

- ***Hx/PE:*** Presents as chronic back pain exacerbated with lumber extension. Both spondylolisthesis and spondylosis may be accompanied by neurologic dysfunction and palpable step-off in the lumbosacral area.
- ***Dx:*** Primarily based on history/PE. Patients can follow prescribed bed rest for 2 weeks to see if there is a resolution of symptoms. If symptoms persist or if LBP danger signs are present (eg, night pain, neurologic symptoms), imaging should be sought.
- ***Tx:*** Mainly centered around rest, symptom control (eg, stretching exercises), and close follow-up. However, if patients start to exhibit signs of neurologic injury (eg, radiculopathy), a spine surgery consult should be obtained.
- Prognosis/complications: Usually complete recovery. Long-term complications from surgery include spinal canal stenosis and disk degeneration.

HIGH-YIELD FACTS IN

NEUROLOGY

- Clinical Neuroanatomy
  - BRAIN
  - CIRCLE OF WILLIS AND ARTERIAL SUPPLY/VENOUS DRAINAGE OF BRAIN
  - MENINGES
  - LUMBAR PUNCTURE
  - PERIPHERAL AND CRANIAL NERVES
  - REFLEXES
- Spinal Cord
- Headaches
  - MIGRAINE HEADACHE
  - CLUSTER HEADACHE
  - TENSION-TYPE HEADACHE
  - SECONDARY HEADACHES
  - TRIGEMINAL NEURALGIA
- Vascular Disorders
  - TRANSIENT ISCHEMIC ATTACK
  - STROKE
  - SUBARACHNOID HEMORRHAGE
  - INTRACEREBRAL HEMORRHAGE
  - SUBDURAL AND EPIDURAL HEMORRHAGE
  - CAVERNOUS SINUS THROMBOSIS
- Coma and Encephalopathy
- Aphasia
  - BROCA/EXPRESSIVE APHASIA
  - WERNICKE/RECEPTIVE APHASIA
- Seizure Disorders
  - CLASSIFICATION OF SEIZURE
  - STATUS EPILEPTICUS
- Vertigo
  - BENIGN PAROXYSMAL POSITIONAL VERTIGO
  - ACUTE PERIPHERAL VESTIBULOPATHY (LABYRINTHITIS OR VESTIBULAR NEURITIS)
  - MÉNIÈRE DISEASE
- CNS Infections
  - MENINGITIS
  - CRYPTOCOCCAL MENINGITIS
  - TOXOPLASMOSIS
  - ENCEPHALITIS

BRAIN ABSCESS

Disorders of Neuromuscular Junction

MYASTHENIA GRAVIS
LAMBERT-EATON MYASTHENIC SYNDROME
BOTULISM

Demyelinating Disorders

MULTIPLE SCLEROSIS
GUILLIAN-BARRÉ SYNDROME

Neurodegenerative Disorders

DEMENTIA
ALZHEIMER DISEASE
VASCULAR DEMENTIA
FRONTOTEMPORAL DEMENTIA (PICK DISEASE)
NORMAL-PRESSURE HYDROCEPHALUS
CREUTZFELDT-JAKOB DISEASE
LEWY BODY DEMENTIA

Movement Disorders

HUNTINGTON DISEASE
PARKINSON DISEASE AND PARKINSONISM
AMYOTROPHIC LATERAL SCLEROSIS
RESTLESS LEGS SYNDROME
TREMORS
WILSON DISEASE OR HEPATOLENTICULAR DEGENERATION

Neoplasms

Neurocutaneous Disorders

NEUROFIBROMATOSIS
TUBEROUS SCLEROSIS
STURGE-WEBER SYNDROME
VON HIPPLE-LINDAU SYNDROME
ATAXIA-TELANGIECTASIA

Other Neurologic Diseases

NUTRITIONAL DEFICIENCIES
IDIOPATHIC INTRACRANIAL HYPERTENSION

Ophthalmology

VISUAL FIELD DEFECTS
HORDEOLUM
CHALAZION
BLEPHARITIS
CORNEAL ABRASION
PRESEPTAL (PERIORBITAL) CELLULITIS
ORBITAL (POSTSEPTAL) CELLULITIS

CONJUNCTIVITIS
ACUTE DACRYOCYSTITIS
HERPES SIMPLEX KERATITIS
CONTACT LENS KERATITIS
UVEITIS
REFRACTIVE ERRORS
PRESBYOPIA
GLAUCOMA
CATARACT
AGE-RELATED MACULAR DEGENERATION
RETINAL VASCULAR OCCLUSION
OPTIC NEURITIS
RETINAL DETACHMENT
DIABETIC RETINOPATHY
HYPERTENSIVE RETINOPATHY
RETINITIS PIGMENTOSA
PAPILLEDEMA
LEUKOCORIA
RELATIVE AFFERENT PUPILLARY DEFECT
HORNER SYNDROME
ORBITAL BLOWOUT FRACTURE
CAVERNOUS SINUS SYNDROME
INTRANUCLEAR OPHTHALMOPLEGIA

Otology
OTITIS MEDIA
OTITIS EXTERNA
MALIGNANT OTITIS EXTERNA
SENSORINEURAL HEARING LOSS
CONDUCTIVE HEARING LOSS

CLINICAL NEUROANATOMY

BRAIN

The brain is organized into diverse areas that allow it to carry out a wide variety of specific functions. Most of the sensory areas are located posterior to the central sulcus, whereas the motor areas are located anterior to the central sulcus. The visual cortex is in the occipital lobe, and the auditory cortex is in the temporal lobe. Further details are shown in Figure 2.9-1.

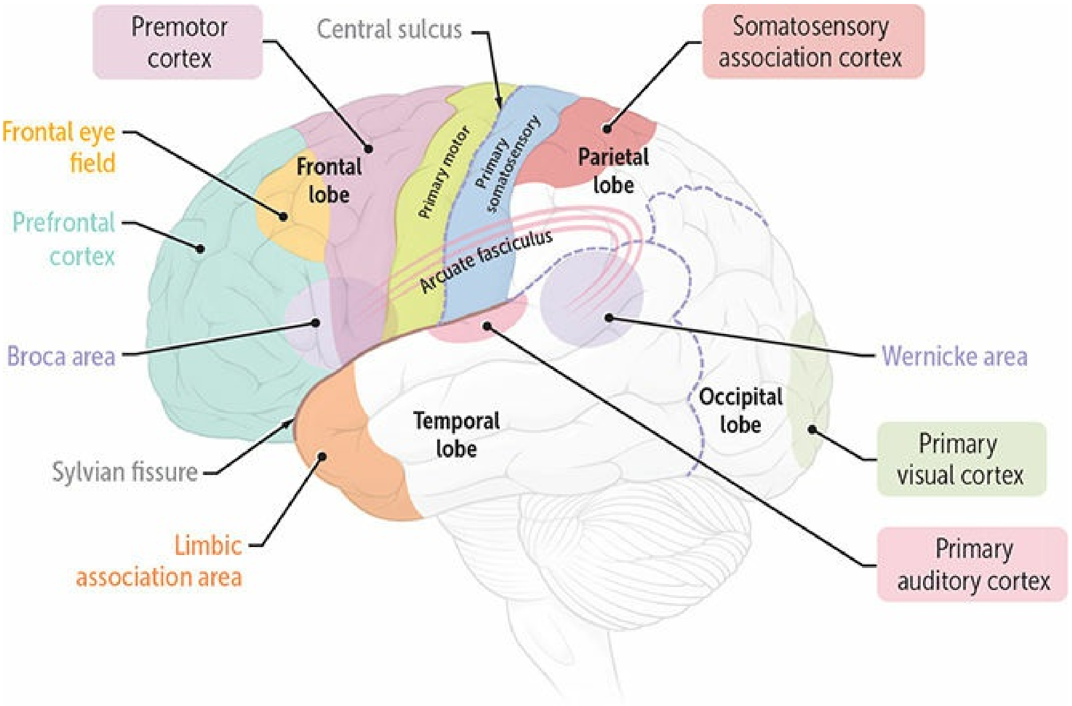

Premotor cortex
Central sulcus
Somatosensory association cortex
Frontal eye field
Prefrontal cortex
Frontal lobe
Primary motor
Primary somatosensory
Parietal lobe
Arcuate fasciculus
Broca area
Wernicke area
Occipital lobe
Temporal lobe
Sylvian fissure
Primary visual cortex
Limbic association area
Primary auditory cortex

FIGURE 2.9-1. **Cortical map of the brain.** (Reproduced with permission from USMLE-Rx.com.)

The primary motor and somatosensory cortices can also be mapped to represent specific parts of the body. This is called the *homunculus*. Note the disproportionate representation of various areas of the body, based on the innervation density of nerve cells to these areas and the complexity of their functions (Fig. 2.9-2).

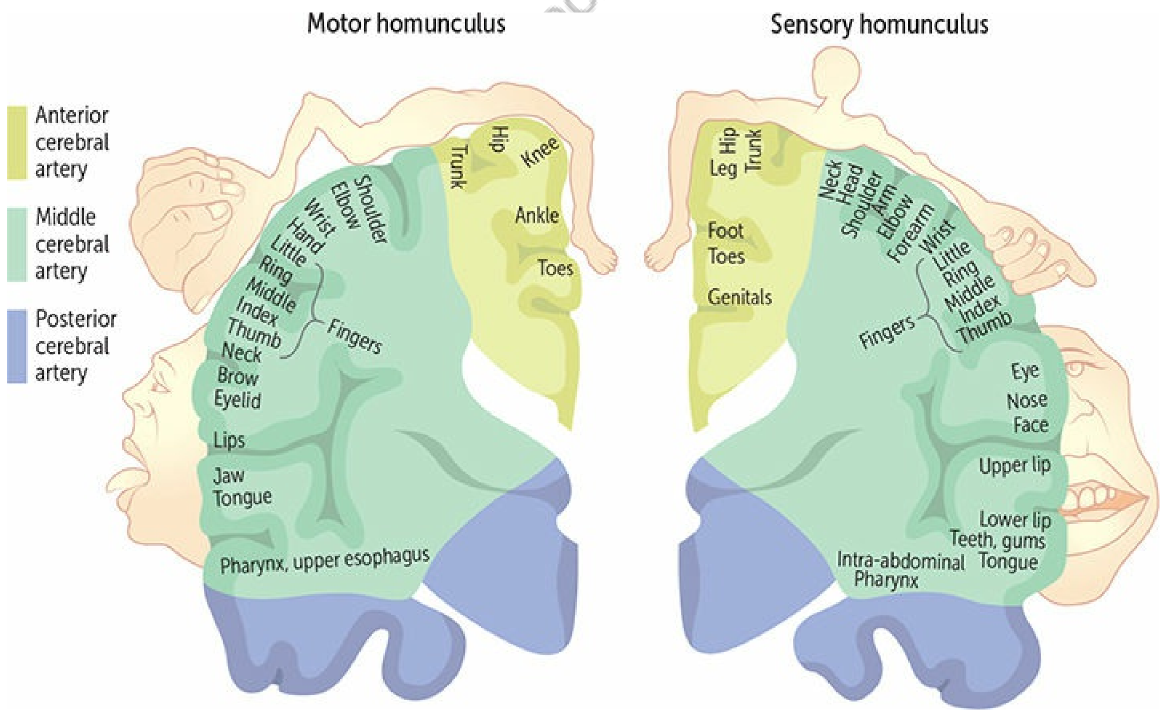

Motor homunculus
Sensory homunculus
Anterior cerebral artery
Middle cerebral artery
Posterior cerebral artery
Trunk
Hip
Knee
Ankle
Toes
Shoulder
Elbow
Wrist
Hand
Little
Ring
Middle
Index
Thumb
Fingers
Neck
Brow
Eyelid
Lips
Jaw
Tongue
Pharynx, upper esophagus
Hip
Trunk
Leg
Foot
Toes
Genitals
Neck
Head
Shoulder
Arm
Elbow
Forearm
Wrist
Little
Ring
Middle
Index
Thumb
Fingers
Eye
Nose
Face
Upper lip
Lower lip
Teeth, gums
Tongue
Intra-abdominal
Pharynx

FIGURE 2.9-2. **Homunculus.** (Modified with permission from USMLE-Rx.com.)

Neuroimaging helps assess complications of intracranial pathology such as herniation syndromes, as shown in Figure 2.9-3. The most common types of brain herniation include:

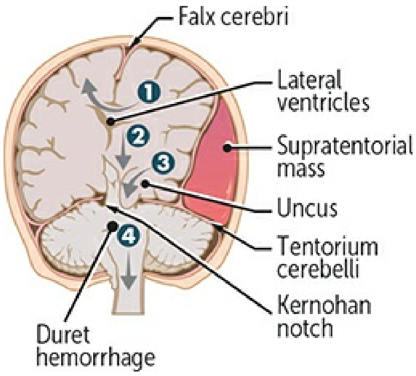


FIGURE 2.9-3. **Herniation syndromes.** (Reproduced with permission from USMLE-Rx.com.)

- Cingulate (subfalcine) herniation under the falx cerebri, which can compress the anterior cerebral artery.
- Central/downward transtentorial herniation that leads to brainstem displacement with rupture of paramedian basilar artery branches and Duret hemorrhages in the brainstem. It is usually fatal.
- Uncal transtentorial herniation, or herniation of the medial temporal lobe: Early herniation leads to ipsilateral blown pupil (secondary to ipsilateral cranial nerve [CN] III compression) and contralateral hemiparesis. Late presentation leads to coma and Kernohan phenomenon (ipsilateral hemiparesis due to contralateral compression against the Kernohan notch and a subsequent misleading contralateral blown pupil).
- Cerebellar tonsillar herniation into the foramen magnum, which compresses the brainstem and may lead to coma and death.

KEY FACT

A "blown pupil" suggests ipsilateral third nerve compression secondary to uncal herniation.

CIRCLE OF WILLIS AND ARTERIAL SUPPLY/VENOUS DRAINAGE OF BRAIN

There are three major blood vessels arising from the circle of Willis to supply the brain, and the respective cortical territories supplied by them are shown in Figure 2.9-4.

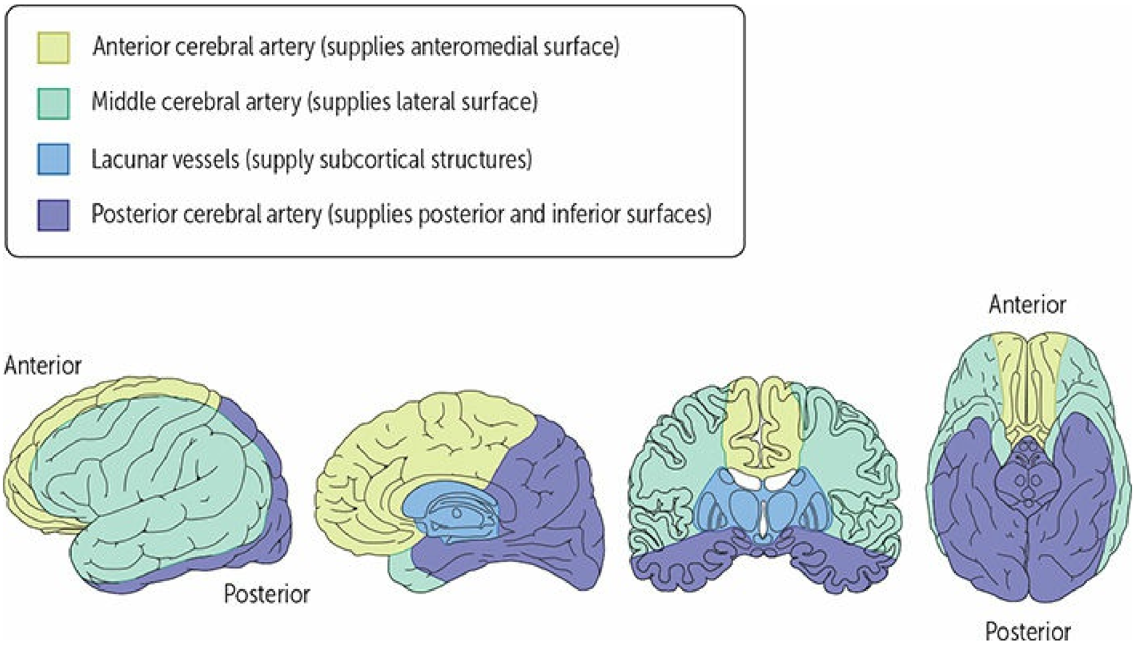

Anterior cerebral artery (supplies anteromedial surface)
Middle cerebral artery (supplies lateral surface)
Lacunar vessels (supply subcortical structures)
Posterior cerebral artery (supplies posterior and inferior surfaces)
Anterior
Posterior
Anterior
Posterior

FIGURE 2.9-4. **Cortical blood supply by various arteries.** (Reproduced with permission from USMLE-Rx.com.)

The various branches of the circle of Willis and their divisions into the anterior and posterior circulations are shown in Figure 2.9-5.

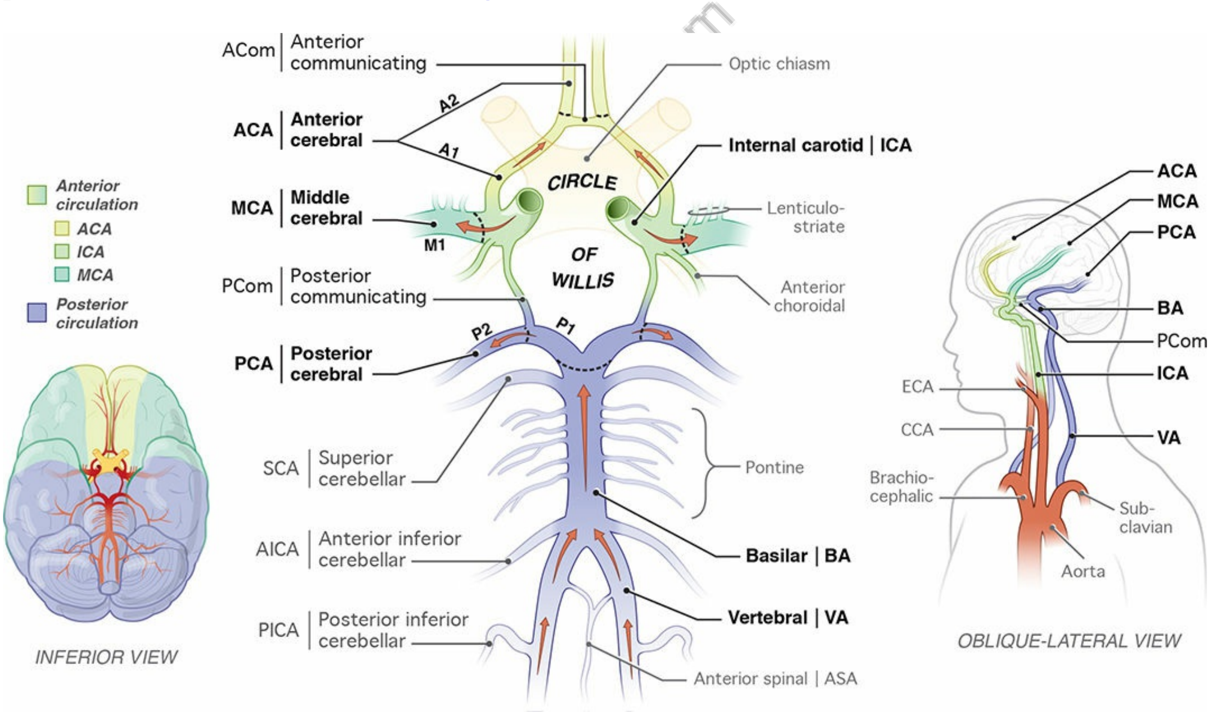

ACom | Anterior communicating
ACA | Anterior cerebral
MCA | Middle cerebral
PCom | Posterior communicating
PCA | Posterior cerebral
SCA | Superior cerebellar
AICA | Anterior inferior cerebellar
PICA | Posterior inferior cerebellar
A2
A1
M1
P2
P1
CIRCLE OF WILLIS
Optic chiasm
Internal carotid | ICA
Lenticulo-striate
Anterior choroidal
Pontine
Basilar | BA
Vertebral | VA
Anterior spinal | ASA
Anterior circulation
ACA
ICA
MCA
Posterior circulation
INFERIOR VIEW
ACA
MCA
PCA
BA
PCom
ICA
VA
ECA
CCA
Brachio-cephalic
Sub-clavian
Aorta
OBLIQUE-LATERAL VIEW

FIGURE 2.9-5. **Circle of Willis.** (Reproduced with permission from USMLE-Rx.com.)

The most common sites of aneurysm are in the anterior circulation. The three most common sites (~85% of all intracranial aneurysms) are the junction of the anterior communicating artery with the anterior cerebral artery (35%), junction of the posterior communicating artery with the internal carotid artery (30%), and bifurcation of the middle cerebral artery (22%).

MENINGES

The brain and the spinal cord are protected by layers of membranous covering (meninges) that protect them from mechanical damage and help provide a structural framework for the vasculature. There are three layers of meninges: the outermost dura mater, the innermost pia mater, and the one in between called the arachnoid mater, as shown in Figure 2.9-6.

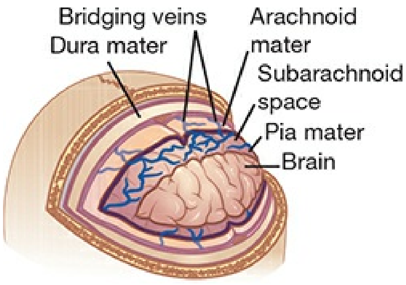


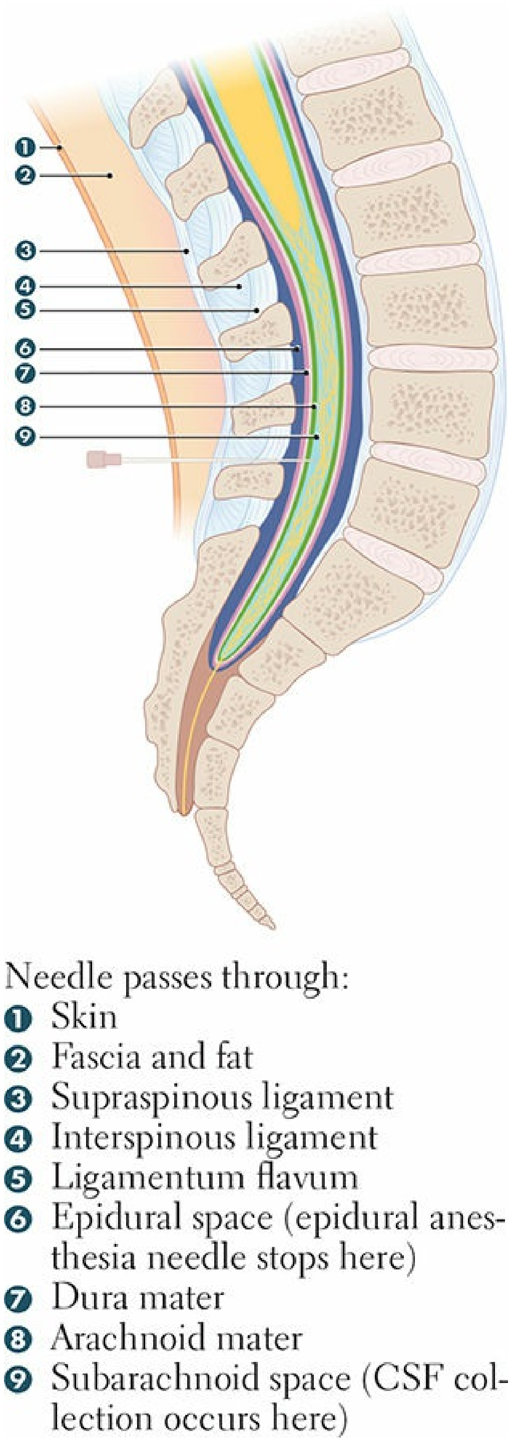
FIGURE 2.9-6. Different layers of meninges. (Modified with permission from USMLE-Rx.com.)

- **Dura mater:** Two-layered thick connective tissue sheath that houses the dural venous sinuses, which empty into the internal jugular veins. Blood supply comes from the middle meningeal artery and vein. Nerve supply is from CN V (anterior and middle cranial fossa), CN X (posterior fossa), sympathetics, and C1–C3 cervical nerves.
- **Arachnoid mater:** Avascular middle layer that gives rise to small projections called *arachnoid granulations,* which allow cerebrospinal fluid (CSF) to re-enter the circulation. CSF is present underneath this layer of the meninges in a space called the subarachnoid space.
- **Pia mater:** Innermost layer of the meninges that is very thin and tightly adhered to the surface of the brain and spinal cord.

The pia mater and the arachnoid mater are commonly referred to collectively as the *leptomeninges.* Meningitis refers to inflammation of these layers.

LUMBAR PUNCTURE

Lumbar punctures are one of the most commonly used examinations to diagnose a central nervous system (CNS) problem. They are commonly performed distal to the inferior tip of the spinal cord, below the level of the lumbar (L)1–L2 vertebrae in adults (L3–4 and L4–5 are common locations) and below the L4 vertebra in children. Lumbar puncture entails piercing the subarachnoid space (which extends to the lower border of the sacral [S2] vertebra and contains the CSF). The layers pierced by the needle to enter this space are shown in Figure 2.9-7.



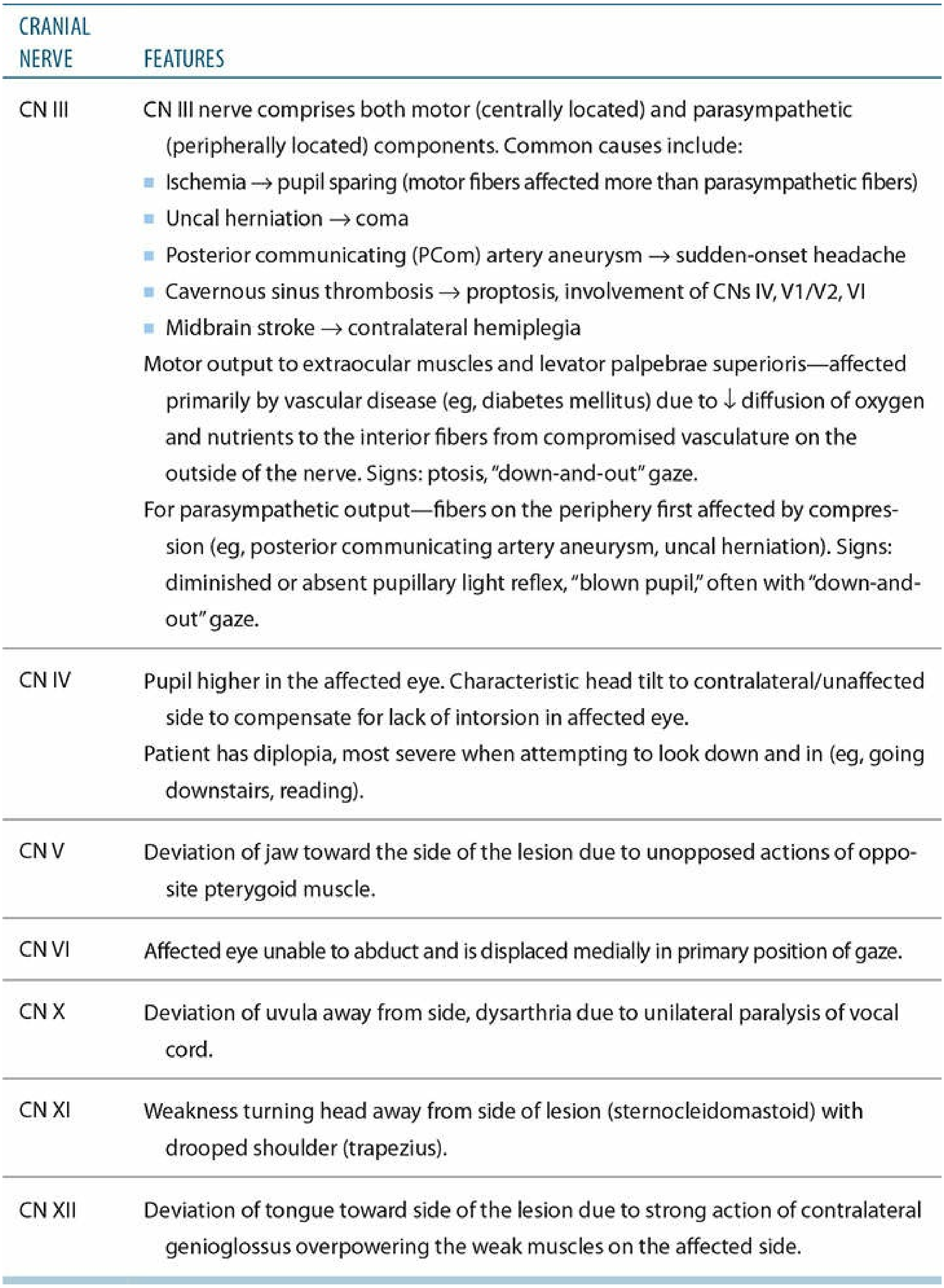
Needle passes through:
- ❶ Skin
- ❷ Fascia and fat
- ❸ Supraspinous ligament
- ❹ Interspinous ligament
- ❺ Ligamentum flavum
- ❻ Epidural space (epidural anesthesia needle stops here)
- ❼ Dura mater
- ❽ Arachnoid mater
- ❾ Subarachnoid space (CSF collection occurs here)

FIGURE 2.9-7. Structures pierced during lumbar puncture. (Modified with permission from USMLE-Rx.com.)

PERIPHERAL AND CRANIAL NERVES

Some commonly tested CN lesions appear in Table 2.9-1.

TABLE 2.9-1. Cranial Nerve Lesions

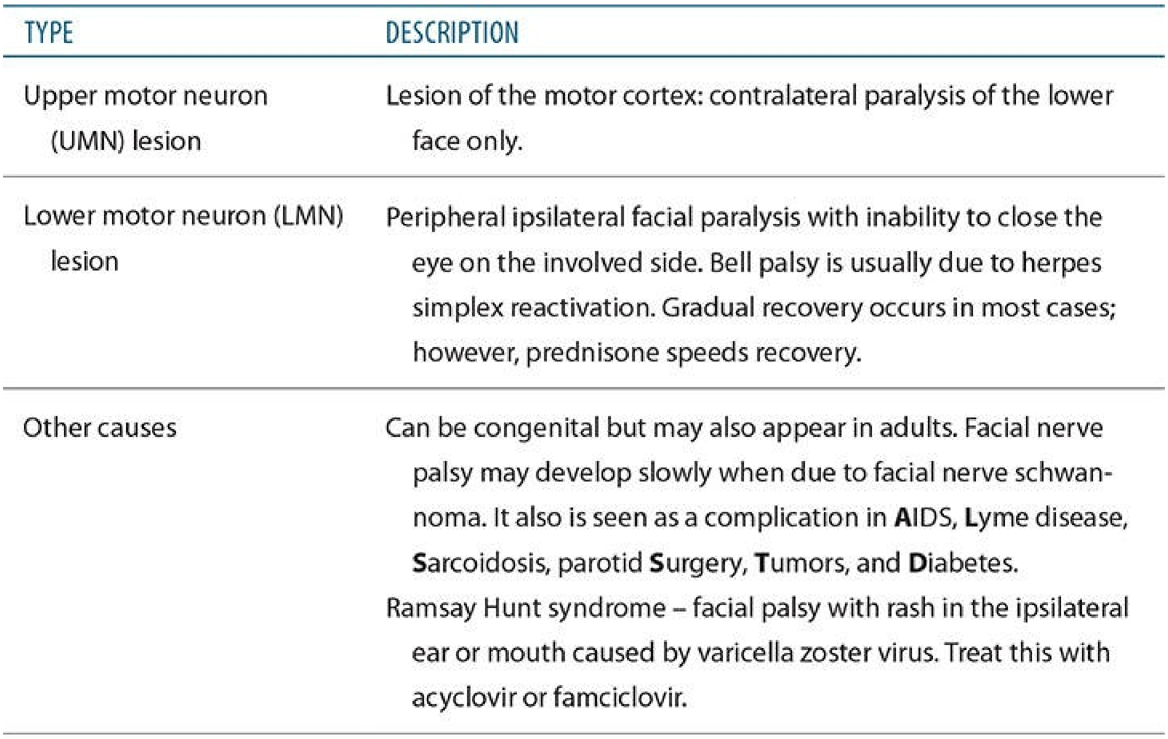


CRANIAL NERVE	FEATURES
CN III	CN III nerve comprises both motor (centrally located) and parasympathetic (peripherally located) components. Common causes include: ▪ Ischemia → pupil sparing (motor fibers affected more than parasympathetic fibers) ▪ Uncal herniation → coma ▪ Posterior communicating (PCom) artery aneurysm → sudden-onset headache ▪ Cavernous sinus thrombosis → proptosis, involvement of CNs IV, V1/V2, VI ▪ Midbrain stroke → contralateral hemiplegia Motor output to extraocular muscles and levator palpebrae superioris—affected primarily by vascular disease (eg, diabetes mellitus) due to ↓ diffusion of oxygen and nutrients to the interior fibers from compromised vasculature on the outside of the nerve. Signs: ptosis, "down-and-out" gaze. For parasympathetic output—fibers on the periphery first affected by compression (eg, posterior communicating artery aneurysm, uncal herniation). Signs: diminished or absent pupillary light reflex, "blown pupil," often with "down-and-out" gaze.
CN IV	Pupil higher in the affected eye. Characteristic head tilt to contralateral/unaffected side to compensate for lack of intorsion in affected eye. Patient has diplopia, most severe when attempting to look down and in (eg, going downstairs, reading).
CN V	Deviation of jaw toward the side of the lesion due to unopposed actions of opposite pterygoid muscle.
CN VI	Affected eye unable to abduct and is displaced medially in primary position of gaze.
CN X	Deviation of uvula away from side, dysarthria due to unilateral paralysis of vocal cord.
CN XI	Weakness turning head away from side of lesion (sternocleidomastoid) with drooped shoulder (trapezius).
CN XII	Deviation of tongue toward side of the lesion due to strong action of contralateral genioglossus overpowering the weak muscles on the affected side.

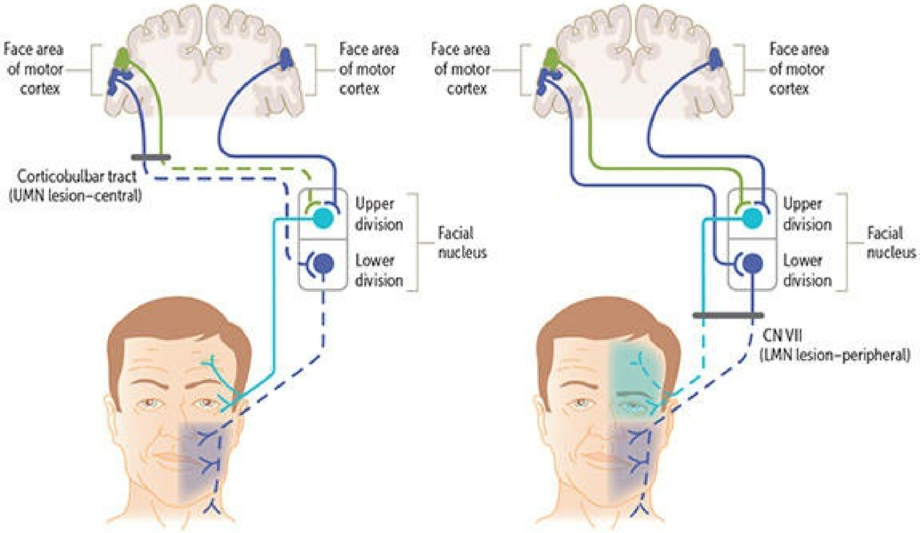
Facial Nerve Palsy

Facial weakness is broadly categorized into either upper or lower motor neuron weakness. UMN facial weakness is most often due to a stroke in the contralateral hemisphere while LMN facial weakness is most often due to a lesion of the facial nerve itself (Table 2.9-2).

TABLE 2.9-2. Facial Nerve Lesions



TYPE	DESCRIPTION
Upper motor neuron (UMN) lesion	Lesion of the motor cortex: contralateral paralysis of the lower face only.
Lower motor neuron (LMN) lesion	Peripheral ipsilateral facial paralysis with inability to close the eye on the involved side. Bell palsy is usually due to herpes simplex reactivation. Gradual recovery occurs in most cases; however, prednisone speeds recovery.
Other causes	Can be congenital but may also appear in adults. Facial nerve palsy may develop slowly when due to facial nerve schwannoma. It also is seen as a complication in **A**IDS, **L**yme disease, **S**arcoidosis, parotid **S**urgery, **T**umors, and **D**iabetes. Ramsay Hunt syndrome – facial palsy with rash in the ipsilateral ear or mouth caused by varicella zoster virus. Treat this with acyclovir or famciclovir.


Face area of motor cortex
Face area of motor cortex
Corticobulbar tract (UMN lesion–central)
Upper division
Lower division
Facial nucleus
Face area of motor cortex
Face area of motor cortex
Upper division
Lower division
Facial nucleus
CN VII (LMN lesion–peripheral)

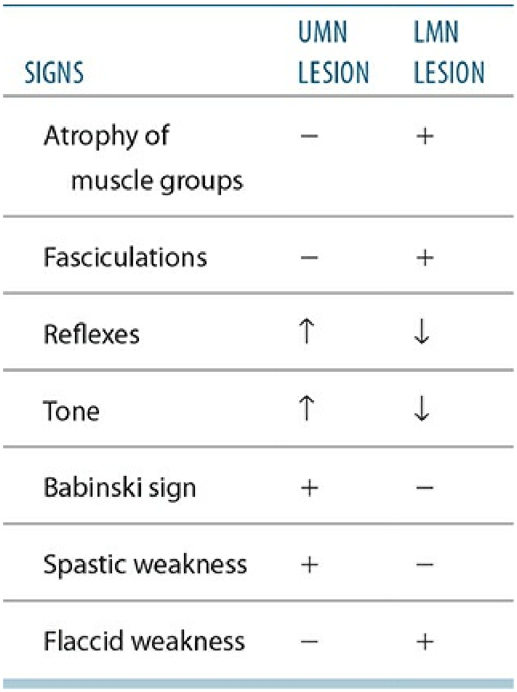
Facial nerve palsy: upper motor neuron lesion *(left)* and lower motor neuron lesion *(right)*.

Adapted with permission from Le T et al. *First Aid for the USMLE Step 1 2022*. New York, NY: McGraw-Hill Education; 2022. Images reproduced with permission from USMLE-Rx.com.

UMN vs LMN

When differentiating upper versus lower motor neuron symptoms, remember that with an upper motor neuron (UMN) type lesion, everything goes "up." However, with a lower motor neuron (LMN) type lesion, everything goes "down." See Table 2.9-3 for differentiating features.

TABLE 2.9-3. **UMN vs LMN Lesions**

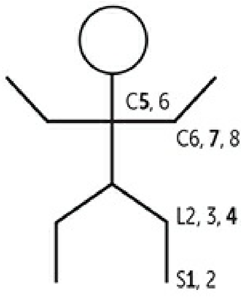


SIGNS	UMN LESION	LMN LESION
Atrophy of muscle groups	–	+
Fasciculations	–	+
Reflexes	↑	↓
Tone	↑	↓
Babinski sign	+	–
Spastic weakness	+	–
Flaccid weakness	–	+

REFLEXES

To identify lesions in various spinal segments, reflexes are tested clinically. Reflexes can act as a guide to assess the level of spinal cord injury. Some important reflexes are given in Table 2.9-4.

TABLE 2.9-4. **Commonly Tested Reflexes**



Important reflexes

The most important reflexes count up in order. The main nerve roots are given in **bold**:

- Achilles reflex: **S1**, S2
- Patellar reflex: L2–**L4**
- Biceps and brachioradialis reflexes: **C5**, C6
- Triceps reflex: C6, **C7**, C8

Additionally, the following reflexes can be assessed:

- Cremasteric reflex: L1, L2
- Anal wink reflex: S3, S4

Reflex grading:
0 = absent
1+ = hypoactive
2+ = normal
3+ = hyperactive
4+ = clonus

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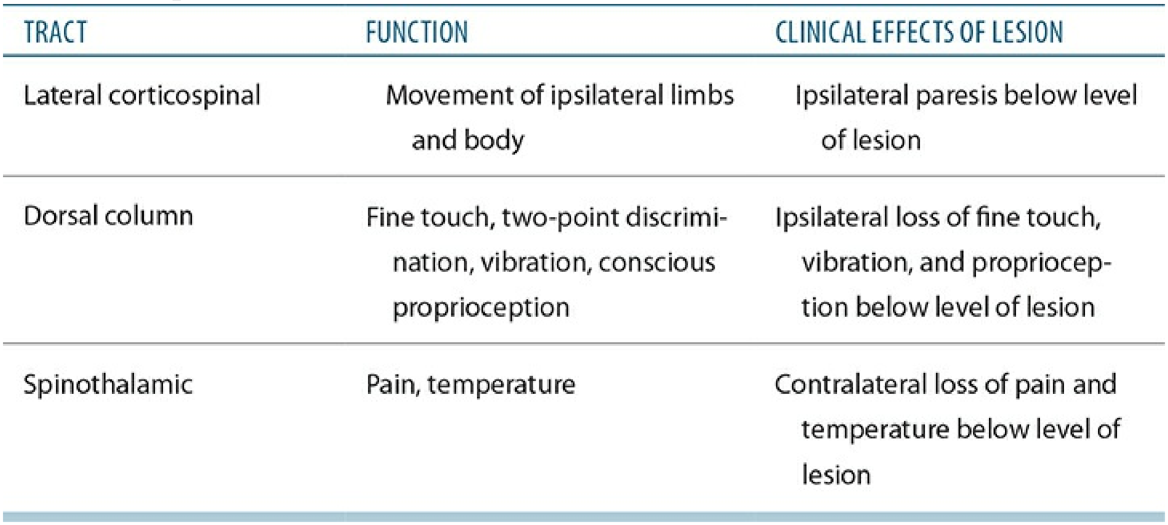
SPINAL CORD

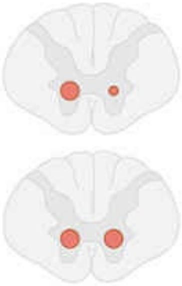
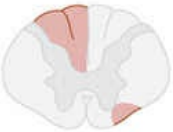
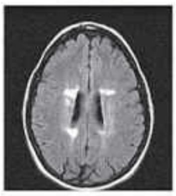
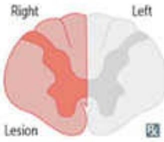
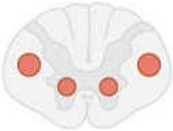
Tables 2.9-5 and 2.9-6 highlight critical aspects of clinical neuroanatomy, including the clinical presentation of common spinal cord lesions. The alignment of these tracts in a spinal cord, when examined on a cross-section, is shown in Figure 2.9-8.

TABLE 2.9-5. **Spinal Tract Functions**



TRACT	FUNCTION	CLINICAL EFFECTS OF LESION
Lateral corticospinal	Movement of ipsilateral limbs and body	Ipsilateral paresis below level of lesion
Dorsal column	Fine touch, two-point discrimination, vibration, conscious proprioception	Ipsilateral loss of fine touch, vibration, and proprioception below level of lesion
Spinothalamic	Pain, temperature	Contralateral loss of pain and temperature below level of lesion

TABLE 2.9-6. **Spinal Cord Lesions**

AREA AFFECTED	DISEASE	CHARACTERISTICS
	Poliomyelitis and spinal muscular atrophy	LMN lesions only, caused by destruction of anterior horns; presents with flaccid paralysis. Poliomyelitis is caused by enterovirus (picornavirus, RNA), transmitted via fecal-oral route. Similar lesions and symptoms may occur with West Nile virus infection. Lumbar puncture (LP) shows pleocytosis (neutrophils first and then lymphocytes) with slightly elevated protein and normal glucose. Treatment calls for supportive therapy and rehabilitation. Spinal muscular atrophy (SMA) is due to mutation in *SMN1* and *SMN2* genes. It presents with weakness and muscle wasting in limbs, respiratory, or brainstem muscles. Diagnosis relies on genetic testing (prenatal and postnatal); normal CSF findings and normal creatine kinase (CK) levels. Supportive therapy is the mainstay of treatment.
 	Multiple sclerosis	Can be caused by infections (Epstein-Barr virus [EBV]), immune disorders, environmental factors (eg, vitamin D deficiency), and genetic factors. Leads to focal inflammation and macroscopic plaques with injury to the blood-brain barrier (BBB) and subsequent neurodegeneration. Features: Demyelination involves patchy areas of the subcortical white matter, brainstem, and spinal cord, mostly cervical region. Optic nerve demyelination leads to monocular vision loss. Diagnosis: Clinical + MRI + to rule out other causes. Lesions are disseminated in space and time. Treatment: Glatiramer acetate, fingolimod, interferon-beta preparations, and dimethyl fumarate modify disease course. Treat underlying cause for relapse and symptoms of neurologic issues-course of IV steroids (methylprednisolone) can hasten recovery from flare or relapse.
	Transverse myelitis	Can be an acquired, focal, inflammatory disorder that usually is a part of multiple sclerosis. However, it can occur with infections by enterovirus, HIV, *Mycoplasma, Treponema pallidum,* and others. Presentation: Most commonly in thoracic levels, leads to paraplegia with loss of bladder/bowel function. It can have both UMN and LMN signs. Pathology: Perivascular infiltration, demyelination, and axonal injury. Diagnosis: Exclude cord compression first with MRI and then do LP. Treatment: High-dose intravenous (IV) glucocorticoids, pain management.
	Brown-Séquard hemisection	Caused most commonly by trauma to the spinal cord. Leads to contralateral loss of pain and temperature sensation one to two levels below the lesion and ipsilateral hemiparesis and diminished dorsal column sensation (vibration and proprioception) below the level of the lesion.
	Amyotrophic lateral sclerosis (ALS)	Commonly known as Lou Gehrig disease in the United States and motor neuron disease in the United Kingdom. Combined UMN and LMN deficits with no sensory or oculomotor deficits; both UMN and LMN signs. Commonly presents as asymmetric painless weakness, fasciculations, and eventual atrophy and weakness of arms and legs; fatal. Riluzole treatment has modest benefit by ↓ presynaptic glutamate release. For Lou Gehrig disease, give riluzole.

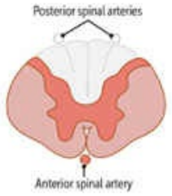
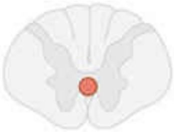
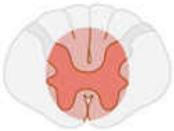
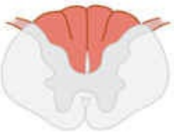
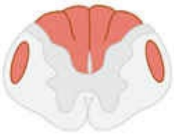
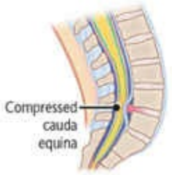
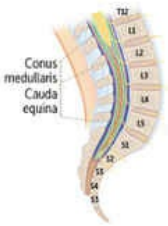
AREA AFFECTED	DISEASE	CHARACTERISTICS
	Complete occlusion of anterior spinal artery	Also called anterior cord syndrome. Spares dorsal columns. Acute onset of sensory-motor dissociation. Location of infarct often at T1–L2 levels, leading to lateral horn injury and associated autonomic dysfunctions such as neurogenic bowel/bladder, orthostatic hypotension, or sexual dysfunction. Associated with abdominal aortic surgery with injury to artery of Adamkiewicz. Diagnosis: MRI. Treatment: Correct aortic dissection or treat vasculitis.
	Syringomyelia	Syrinx (CSF-filled cavity within spinal cord) expands and damages anterior white commissure of spinothalamic tract. Can arise from trauma or tumors; seen in 35% of Chiari malformations. Results in a capelike, bilateral loss of pain and temperature in upper extremities (likely to have painless burn injuries).
	Central cord syndrome	Weakness more pronounced in upper extremities than lower extremities, as the arm/trunk fibers are located more medially within the corticospinal tract and are preferentially affected. Affected sensory losses are due to effect on the decussating spinothalamic tract fibers (bilateral loss of pain and temperature at level of lesion). Caused by hyperextension injuries in individuals >50 years of age or secondary to spinal cord tumors (eg, astrocytomas, ependymomas).
	Tabes dorsalis	Caused by tertiary syphilis. Results from degeneration (demyelination) of dorsal columns and roots (especially at lumbosacral levels) → impaired sensation and proprioception, sharp fleeting pain in the legs, progressive sensory ataxia (inability to sense or feel the legs) → poor coordination. Associated with Charcot joints (repeated unknowing trauma to joint caused by lack of pain), shooting pain, Argyll Robertson pupils. Examination will demonstrate absence of deep tendon reflex and ⊕ Romberg sign.
	Vitamin B_{12} deficiency	Subacute combined degeneration—demyelination of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts; ataxic gait, paresthesia, impaired position and vibration sense.
	Cauda equina syndrome	Neurosurgical emergency. Compression of spinal roots L2 and below, most likely caused by disc herniation, epidural abscess, trauma, or metastatic cancer. Clinical: Saddle anesthesia, loss of bladder and anal sphincter control, and absent knee and ankle jerk reflexes. Diagnosis: MRI and surgical evaluation (in that order).
 Conus medullaris Cauda equina T12 L1 L2 L3 L4 L5 S1 S2 S3 S4 S5	Conus medullaris	Similar to cauda equina with robust parasympathetic dysfunction, but with symmetric weakness. UMN signs will be present (eg, Babinski reflex). Treatment: Same as cauda equina.

Table modified with permission from Le T et al. *First Aid for the USMLE Step 1 2022.* New York, NY: McGraw-Hill Education; 2022. Illustrations reproduced with permission from USMLE-Rx.com. MRI adapted with permission from Dooley MC, Foroozan R. Optic neuritis. *J Ophthalmic Vis Res.* 2010;5(3):182-187.

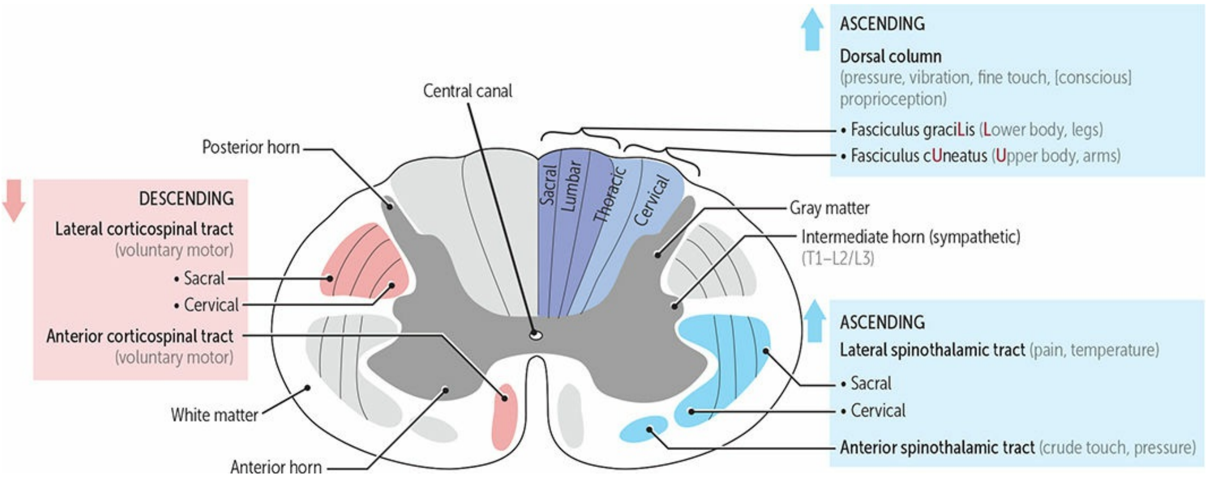

ASCENDING
Dorsal column
(pressure, vibration, fine touch, [conscious] proprioception)
• Fasciculus graciLis (Lower body, legs)
• Fasciculus cUneatus (Upper body, arms)
Central canal
Posterior horn
DESCENDING
Lateral corticospinal tract
(voluntary motor)
• Sacral
• Cervical
Anterior corticospinal tract
(voluntary motor)
White matter
Anterior horn
Sacral
Lumbar
Thoracic
Cervical
Gray matter
Intermediate horn (sympathetic)
(T1–L2/L3)
ASCENDING
Lateral spinothalamic tract (pain, temperature)
• Sacral
• Cervical
Anterior spinothalamic tract (crude touch, pressure)

FIGURE 2.9-8. **Cross-section of spinal cord (thoracic) showing arrangement of various tracts.** (Reproduced with permission from USMLE-Rx.com.)

HEADACHES

Headaches can either be primary/idiopathic (eg, migraine, cluster, tension type) or secondary (resulting from underlying disease, such as tumor or intracranial hemorrhage). The differences in these types of headaches are discussed in Table 2.9-7.

TABLE 2.9-7. **Common Types of Headache**

	MIGRAINE HEADACHE	CLUSTER HEADACHE	TENSION-TYPE HEADACHE
Pattern	Typically unilateral, usually throbbing	Severe pain behind the eye, usually unilateral, and usually in smokers	Bandlike tightening or pressing, typically bilateral
Onset	Preceded by aura in classical type	Without preceding aura and 15- to 180-minute headaches that cluster	Without aura, usually at the end of the day; patient can function during headache
Treatment	Abortive therapy (best initial treatment): Triptans, nonsteroidal anti-inflammatory drugs (NSAIDs) Next step: Prevention with propranolol, topiramate, or nortriptyline	Best initial treatment: 100% oxygen for 15 minutes Next step: Prevention with verapamil	Best initial treatment: NSAIDs, acetaminophen Relaxation therapy, ice packs potentially helpful

MIGRAINE HEADACHE

Recurrent headache disorder with attacks that last 4 to 72 hours. Headache typically unilateral, pulsating, and moderate or severe in intensity and aggravated by routine physical activity. Usually preceded by auras (auditory or visual most common). Affects women more than men; often familial; onset usually by teens to early 20s, but peak age is 30 to 39 years. Linked to changes in vascular tone and neurotransmitters (especially calcitonin gene-related peptide [CGRP]). Triggers: Certain foods (eg, red wine, cheese), fasting, stress, menses, oral contraceptive pills (OCPs), bright light, and disruptions in normal sleep patterns, among others. Increased stroke risk in women with classic migraine headaches who take OCPs and smoke.

Diagnosis

- Based on history and recognition of pattern of headache (usually preceded by an aura and a trigger). Physician should query about past events that may have started the headache at first.

- Recognition of associated features such as nausea, dizziness, light sensitivity, smell changes, and disturbed bowel movements. Headaches typically last 4 to 72 hours (untreated or successfully treated), with two of four characteristics (unilateral, pulsating, moderate/severe pain intensity, aggravated by routine physical activity) and association with nausea/vomiting or photophobia/phonophobia.
- At least five attacks needed for migraine diagnosis.

Treatment

- Avoidance of known triggers
- Abortive therapy, including triptans (after over-the-counter [OTC] nonsteroidal anti-inflammatory drugs [NSAIDs] have failed), alone or in addition to other analgesics such as naproxen. The physician should consider symptomatic treatment for nausea. IV metoclopramide can be used for abortive therapy in the ED. Other treatments include ergots or CGRP antagonists (rimegepant, ubrogepant).
- Prophylaxis for frequent or severe migraines, including anticonvulsants (eg, valproate, topiramate), tricyclic antidepressants ([TCAs], eg, amitriptyline), and β-blockers (propranolol; first-line prevention in pregnant patients). Erenumab blocks CGRP action and has a prophylactic role. Chronic cases may benefit from injection of botulinum toxin.
- Routine aerobic exercise and good sleep hygiene.

CLUSTER HEADACHE

Men are affected more often than women; average age of onset is 25 years. Patients who smoke have a higher risk of this type of headache.

History/PE

- Presents as a brief, excruciating, unilateral, periorbital headache that lasts from 30 minutes to 3 hours, during which time the patient tends to be extremely restless. Patients do not have auras (vs migraine headache).
- Tends to occur in clusters of time, affecting the same part of the head at the same time of day (commonly during sleep) during a certain season of the year.
- Associated autonomic symptoms include ipsilateral lacrimation, conjunctival injection, Horner syndrome, and nasal stuffiness.

KEY FACT

If a 25-year-old man wakes up repeatedly during the night with unilateral periorbital pain associated with ipsilateral lacrimation, think cluster headache.

Diagnosis

Classic presentations with a history of repeated attacks over an extended period do not need imaging. First episodes require a workup (eg, MRI, carotid artery ultrasound) to exclude structural brain lesion or disorders associated with Horner syndrome (eg, carotid artery dissection, cavernous sinus infection).

Treatment

- **Acute therapy:** High-flow O_2 or sumatriptan injection
- **Prophylactic therapy:** Verapamil—first-line treatment, typically prescribed with prednisone (10-day course); alternatives include lithium, valproic acid, and topiramate

TENSION-TYPE HEADACHE

- ***Hx:*** Presents with tight, bandlike pain around the head that is triggered by fatigue or stress. Nonspecific symptoms (eg, anxiety, poor concentration, difficulty sleeping) may also be seen.

KEY FACT

If a 30-year-old woman complains of headaches at the end of the day that worsen with stress and improve with relaxation or massage, think tension-type headache.

- ***Dx:*** Must have at least two of the following characteristics: bilateral location, pressing/tightening quality, mild to moderate intensity, and not aggravated by routine physical activity. The physician should rule out giant cell arteritis in patients >65 years of age with new headaches (usually accompanied by jaw claudication) by obtaining an erythrocyte sedimentation rate (ESR), even if headaches are mild with no associated constitutional or vascular symptoms.
- ***Tx:*** Relaxation, massage, hot baths, and avoidance of exacerbating factors. NSAIDs and acetaminophen are first-line abortive therapy.

SECONDARY HEADACHES

The physician should consider secondary headaches when "red flags" (eg, sudden onset, great severity, nocturnal presentation, age >65 years of age, with focal neurologic symptoms, post–head trauma) are present.

History/PE

- Significant findings include fever or rash (consider meningitis or other infectious causes), jaw claudication (specific for temporal arteritis), or constitutional symptoms such as weight loss (associated with neoplastic, inflammatory, or infectious conditions).
- Photophobia, nausea, vomiting, and neck stiffness can be associated with aneurysmal subarachnoid hemorrhage (SAH) and meningitis caused by meningeal irritation.
- Full general and neurologic examinations, including a funduscopic examination, should occur.
- **Neurologic sequelae:** The physician should look for diplopia, altered mental status or associated symptoms (numbness, weakness, dizziness, ataxia, visual disturbances), papilledema, or pupillary abnormalities (partial CN III palsy or Horner syndrome).

KEY FACT

Headache red flags—First, worst, sudden onset of most severe headache ever; neurologic sequelae; nocturnal headache; morning vomiting; onset of headache >65 or <10 years of age; focal neurologic signs or symptoms; papilledema; headache subsequent to head trauma.

Diagnosis

Based on the etiology.

- **If SAH is suspected:** Procure a head CT without contrast. If CT is negative, perform a lumbar puncture to look for xanthochromia, which, if positive, supports the diagnosis of SAH.
- **In the emergency room, when SAH is suspected:**
  - Check ABCs and Glasgow Coma Scale (GCS). Consider early intubation if required.
  - Treat seizures with benzodiazepines and start fluid infusion to maintain intravascular volume.
  - Obtain a complete blood cell count (CBC) to check for systemic infections.
  - If temporal arteritis is suspected, obtain an ESR.

CT of the head is indicated for "red flag" symptoms.

Q

A 28-year-old woman with no prior medical history presents with throbbing, unilateral headache that is exacerbated by menstruation and minimally relieved by acetaminophen and lying in a dark room. She would like something that would provide more symptomatic relief. What abortive therapy should the physician prescribe?

Treatment

- Directed toward underlying cause of headaches. Some conditions such as SAH may require emergency surgery, whereas cases of temporal arteritis may require steroid use.
- Analgesics administered for pain relief as search for underlying disorders begins.

TRIGEMINAL NEURALGIA

Recurrent, severe, and shocklike shooting or stabbing pain along distributions of the trigeminal nerve (CN V), often triggered by cold, minor trauma, or even chewing food or brushing teeth. The pain is often unilateral. It lasts a maximum of 2 minutes.

- ***Pathophysiology:*** Compression of trigeminal nerve root most common cause. Demyelination occurs in multiple sclerosis.
- ***Dx:*** Clinical, with precipitation by innocuous stimulus and not accounted for by another diagnosis. If bilateral, the physician should suspect multiple sclerosis.
- ***Ddx:*** Herpes zoster–induced trigeminal neuropathy, postherpetic neuropathy.
- ***Tx:*** First line with carbamazepine or oxcarbazepine. Surgery (microvascular decompression and rhizotomy, among various options) is required for refractory cases only.

VASCULAR DISORDERS

TRANSIENT ISCHEMIC ATTACK

A transient ischemic attack (TIA) is a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. Most TIAs last 5 to 10 minutes, but can rarely last up to 24 hours. The highest risk for stroke is on the day following the TIA, a risk estimated with the ABCD^2 score.

Pathophysiology

Embolism, lacunar, or small-vessel obstruction; low flow in a large vessel.

Diagnosis

Based on clinical features of transient attack (transient monocular blindness, aphasia/dysarthria, hemianopia, hemiparesis, or sensory loss).

Treatment

- If symptoms are ongoing and potentially disabling: Emergency evaluation for intravenous (IV) thrombolysis + thrombectomy
- If symptoms resolve or are ongoing but nondisabling: Evaluation with MRI or neurovascular imaging to rule out stroke
- Once cause is identified, a plan is implemented to reduce the risk of future stroke by use of medications (antiplatelet therapy), modification of stroke risk factors (eg, hypertension, diabetes), or carotid endarterectomy

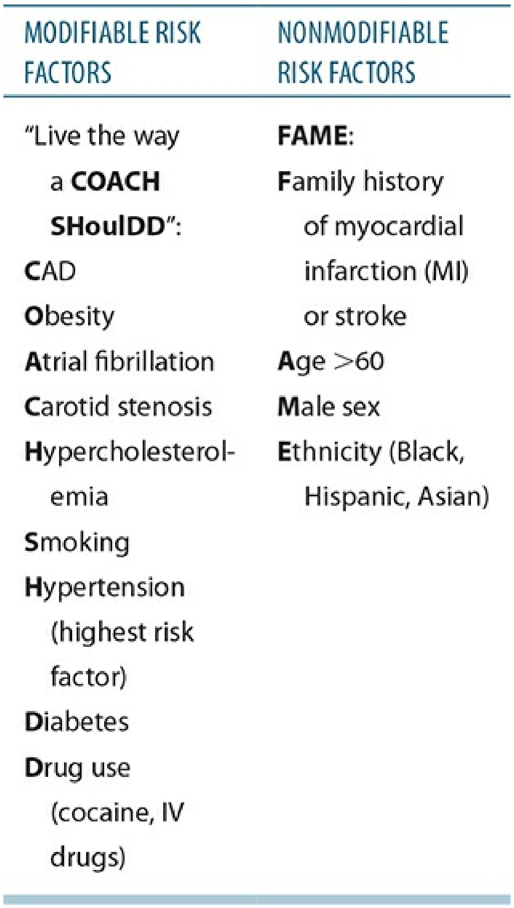
A

This patient’s symptoms are consistent with migraine headaches. The physician should prescribe a triptan for abortive therapy.

STROKE

Disruption of cerebral blood flow leads to death of brain cells, resulting in acute onset of focal neurologic deficits. A stroke can be ischemic (80%) or hemorrhagic (20%). Table 2.9-8 contrasts modifiable and nonmodifiable risk factors associated with stroke. Common etiologies are listed later.

TABLE 2.9-8. Modifiable and Nonmodifiable Risk Factors for Stroke



MODIFIABLE RISK FACTORS	NONMODIFIABLE RISK FACTORS
"Live the way a **COACH** **SHoulDD**": **C**AD **O**besity **A**trial fibrillation **C**arotid stenosis **H**ypercholesterolemia **S**moking **H**ypertension (highest risk factor) **D**iabetes **D**rug use (cocaine, IV drugs)	**FAME**: **F**amily history of myocardial infarction (MI) or stroke **A**ge >60 **M**ale sex **E**thnicity (Black, Hispanic, Asian)

- Atherosclerosis of the extracranial (carotid and vertebral) and intracranial vessels (internal carotid, cerebral, basilar, and vertebral arteries)
- Chronic hypertension, hypercholesterolemia, and diabetes—conditions that can damage perforating vessels supplying deep regions of the brain, leading to lacunar infarcts
- Cardiac or aortic emboli
- **Other causes:** Hypercoagulable states, craniocervical dissection, venous sinus thrombosis, sickle cell anemia, vasculitis (eg, giant cell arteritis)

History/PE

Symptoms are dependent on the vascular territory affected (see Table 2.9-9).

TABLE 2.9-9. **Common Stroke Symptoms by Vessel Territory**

VESSEL TERRITORY	DISTINGUISHING SYMPTOMS
Middle cerebral artery	Contralateral paresis and sensory loss in the face and arm; gaze (eyes deviated towards the lesion); contralateral homonymous hemianopsia Nondominant hemisphere—neglect Dominant hemisphere (90% left side)—aphasia
Anterior cerebral artery	Contralateral paresis and sensory loss in the leg; cognitive or personality changes; urinary incontinence
Posterior cerebral artery	Contralateral homonymous hemianopia with macular sparing. Alexia without agraphia is seen in left PCA strokes Weber syndrome: Occlusion of branch of posterior cerebral artery leading to ipsilateral CN III palsy, contralateral hemiparesis, and parkinsonian rigidity (may not be present if substantia nigra is spared)
Lacunar	Symptoms are pure motor, pure sensory, ataxic hemiparesis, dysarthria, or clumsy hand Underlying pathology includes formation of microatheromas and lipohyalinosis, commonly secondary to hypertension, diabetes, hyperlipidemia, or smoking Strokes affecting the thalamus may cause thalamic pain syndrome several weeks after the event, with hypersensitive pain response over the contralateral affected area of the body
Posterior inferior cerebral artery (PICA) stroke/vertebral (Wallenberg syndrome)	Loss of pain and temperature sensation on ipsilateral face and contralateral body Ipsilateral bulbar weakness/dysarthria Ipsilateral Horner syndrome (ptosis, miosis, and seldom with facial anhidrosis) Vertigo, nystagmus, hiccups
Carotid artery dissection	Sudden headache, neck pain, Horner syndrome Caused by oropharyngeal injury (most common)

Diagnosis

- **Best initial step:** Head CT without contrast (see Fig. 2.9-9A) to differentiate ischemic from hemorrhagic stroke and identify potential candidates for thrombolytic therapy. Ischemic strokes <6 hours old are usually not visible on CT scan.

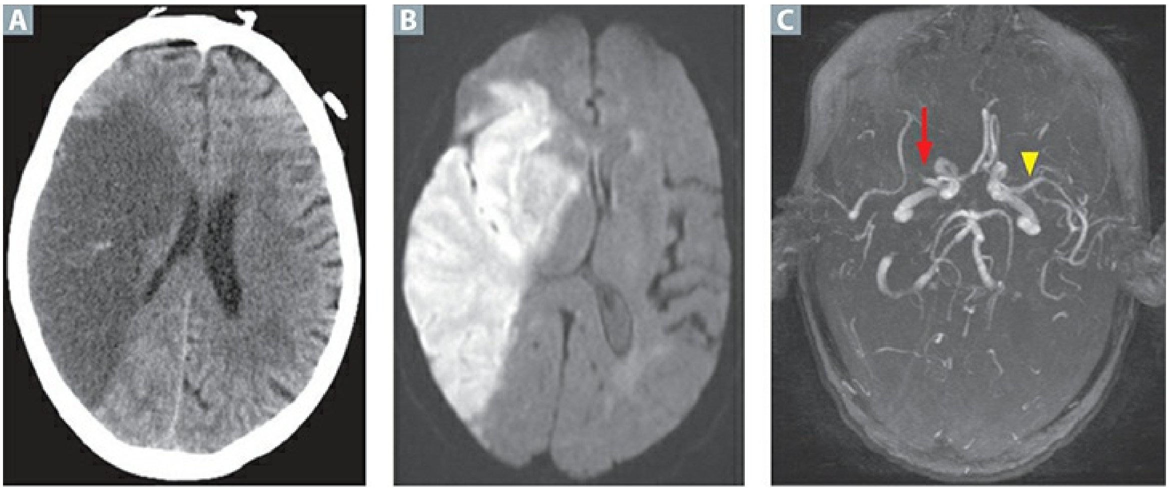


FIGURE 2.9-9. **Acute ischemic stroke.** Acute left hemiparesis in a 62-year-old woman. (A) Noncontrast head CT with loss of gray and white matter differentiation, cortical effacement, and asymmetrically decreased size of the right lateral ventricle in a right middle cerebral artery (MCA) distribution (indicating mass effect). (B) Diffusion-weighted MRI with reduced diffusion in the same distribution, consistent with an acute infarct. Diffusion-weighted sequences are the most sensitive modality for diagnosing an acute ischemic infarct. (C) Magnetic resonance angiography (MRA) shows the cause: an abrupt occlusion of the proximal right MCA *(red arrow)* Compare with the normal left MCA *(yellow arrowhead)*. Note pronounced midline shift evident on both MRI and MRA. (Reproduced with permission from

USMLE-Rx.com.)

- Check blood glucose first. Labs to draw immediately, in case thrombolytic therapy or intervention may be required, include CBC, prothrombin time (PT)/partial thromboplastin time (PTT), cardiac enzymes and troponin, and blood urea nitrogen (BUN)/creatinine.
- Diffusion-weighted MRI (follow-up to CT) (see Fig. 2.9-9B) to identify early ischemic changes not detected on CT.
- Determine underlying cause of stroke:
  - **Cardioembolic:** ECG; echocardiogram; Holter monitor if initial ECG normal.
  - **Thrombotic:** Carotid ultrasonography; MRA; CT angiography (CTA); transcranial Doppler; conventional angiography (see Fig. 2.9-9C).
  - **Other potential causes that should be worked up if there is a high index of suspicion:** Hypercoagulable states; sickle cell disease; vasculitis.

MNEMONIC

Contraindications to tPA therapy (major ones italicized)—

SAMPLE STaGES

__S__troke or head trauma within the last 3 months

***A**nticoagulation with INR >1.7 or prolonged PTT

MI in past 3 months

Prior intracranial hemorrhage

Low platelet count (<100,000/mm^3)

***E**levated BP: Systolic >185 mm Hg or diastolic >110 mm Hg

Major __S__urgery in the past 14 days

TIA (mild symptoms or rapid improvement of symptoms) within 6 months

__G__I or urinary bleeding in the past 21 days or glucose <50 mg/dL

***E**levated (>400 mg/dL) or ↓ (<50 mg/dL) blood glucose

Seizures present at onset of stroke

*If values can be corrected using appropriate treatment before the 3- to 4.5-hour period, consider tPA treatment.

Acute Treatment

Hemorrhagic stroke: See intracerebral hemorrhage discussion.

Ischemic stroke, prehospital: Assessment by first-aid providers and information provided to health care providers in a timely manner prevent complications.

Ischemic stroke, hospital (emergency department):

- Airway support for patients with low GCS (<8) or with bulbar dysfunction.
- Supplemental oxygen to keep SpO_2 >94% only in hypoxic patients.
- Treatment of hypotension for adequate organ perfusion.
- Use of National Institutes of Health Stroke Scale (NIHSS) for diagnosis and assessment.
- Emergency brain imaging on hospital arrival: Noncontrast computed tomography (NCCT) head is investigation of choice.
- Assessment of blood glucose levels and treatment to keep levels between 140 and 180

mg/dL.

- IV alteplase indicated in patients without contraindications; consideration of mechanical thrombectomy. Give alteplase even if thrombectomy is being considered (especially for anterior large vessel occlusions within 24 hours of presentation).
- Thrombolytics (tissue plasminogen activators [tPAs]) if <3 to 4.5 hours since onset of stroke and no bleeding or absolute contraindications. Permissive hypertension is allowed in stroke for perfusion of ischemic area, but patient's systolic blood pressure (SBP) must be <185 and diastolic blood pressure (DBP) <110 mm Hg for tPA.
- Acetylsalicylic acid (ASA) if >3 hours since onset of stroke/TIA.
- If BP is high but patient is eligible for alteplase, lowering of BP to <185/110 mm Hg slowly before therapy initiation. Use labetalol, nicardipine, or clevidipine.
- Treatment of high (>200 mm Hg SBP or >120 mm Hg DBP) or low BP prior to initiating treatment for stroke. Raised BP can lead to further injury (cerebral edema, hemorrhagic transformation, or expansion of hematoma), whereas a low BP can lead to further infarction and perihematomal ischemia. Treatment goals include:
  - Before tPA: <185/110 mm Hg
  - After and within 24 hours of tPA administration or during and after 24 hours of endovascular treatment: <185/105 mm Hg
  - Failed reperfusion: Maintenance of SBP >150 mm Hg
  - Successful reperfusion or hemorrhagic conversion: SBP <140 mm Hg
- If BP >220/120 mm Hg, lowering of BP by 15% in first 24 hours after stroke
- If BP >140/90 mm Hg and neurologically stable, commencement of antihypertensive therapy during hospitalization
- Check of baseline ECG, troponin
- Investigation for cause of hyperthermia (>38°C)
- Monitor for signs and symptoms of brain swelling, ↑ intracranial pressure (ICP), and herniation. Treat by elevating head-end of the bed to 30°, starting hypertonic saline or mannitol, and hyperventilating the patient.
- Prevention and treatment of poststroke complications, such as aspiration pneumonia, urinary tract infection (UTI), and deep vein thrombosis (DVT)

Preventive and Long-Term Treatment

- Hypertension management (DBP <80 mm Hg)
- Diabetes management (blood sugar level approximately 100 mg/dL)
- Blood lipids management with a statin
- ASA or clopidogrel
- Diet, exercise
- For cardioembolic strokes, anticoagulation. In new atrial fibrillation (AF) or hypercoagulable states, the target international normalized ratio (INR) is 2 to 3. In cases involving a prosthetic valve, the target INR is 2.5 to 3.5
- For vascular pathology (pipe failure), antiplatelet medication
- **Carotid endarterectomy:** If stenosis is >60% in symptomatic patients or >70% in asymptomatic patients (contraindicated in 100% occlusion; see Fig. 2.9-10). Benefits may also occur in lower absolute percent stenosis; the physician should use clinical judgment when answering these questions

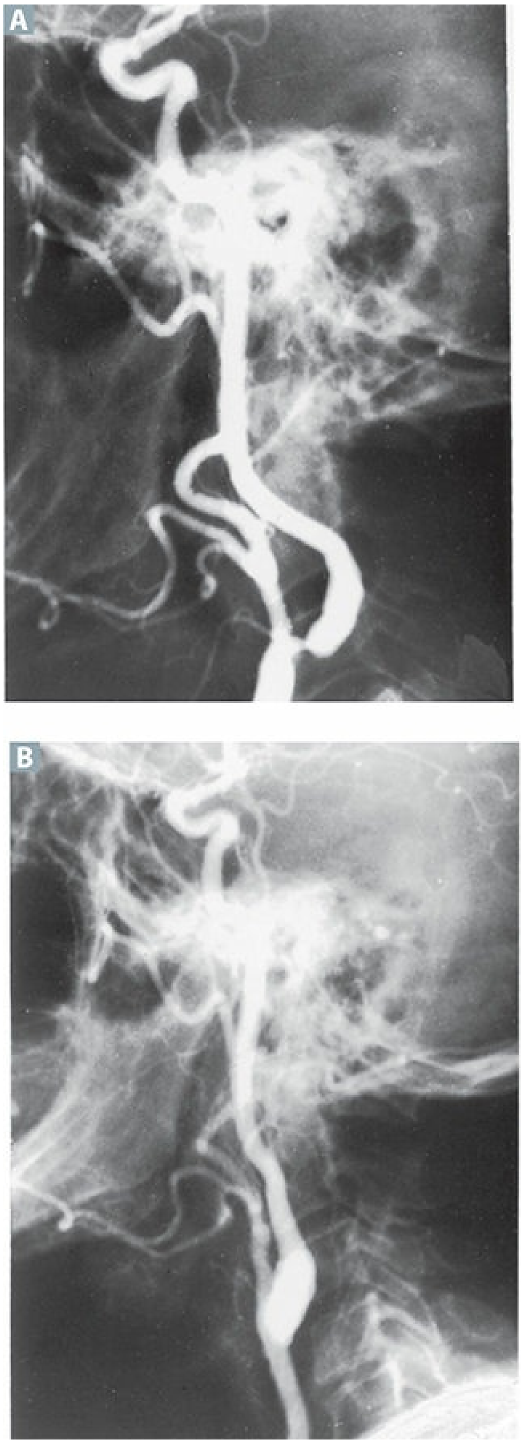


FIGURE 2.9-10. **Vascular studies preendarterectomy and postendarterectomy.** (A) Carotid arteriogram showing stenosis of the proximal internal carotid artery. (B) Postoperative arteriogram with restoration of the normal luminal size following endarterectomy. (Reproduced with permission from Way LW. *Current Surgical Diagnosis & Treatment*. 10th ed. Stamford, CT: Appleton & Lange; 1994.)

SUBARACHNOID HEMORRHAGE

Etiologies of SAH include ruptured saccular aneurysms (berry aneurysms), arteriovenous malformation (AVM), and trauma.

History/PE

- Aneurysmal SAH presents with an abrupt-onset, intensely painful “thunderclap” headache, often followed by neck stiffness (caused by meningeal irritation). Other signs of meningeal irritation, including photophobia, nausea/vomiting, and meningeal stretch signs (Kernig and Brudzinski signs), can also be seen.
- More than one third of patients will give a history of a “sentinel bleed” (“warning leak”) days to weeks before presentation.
- In the absence of neurosurgical intervention, rapid development of obstructive hydrocephalus or seizures often leads to ↓ arousal or frank coma and death.

KEY FACT

SAH = “the worst headache of my life” with sudden onset.
Migraine = a gradually worsening headache (peak intensity >30 minutes)

KEY FACT

Xanthochromia (blood on an LP) is seen in two situations—herpes simplex virus (HSV) encephalitis and SAH.

Diagnosis

- Immediate head CT without contrast subarachnoid space (greatest sensitivity with 6 hours of symptoms; see Fig. 2.9-11A). to look for blood in the subarachnoid space.

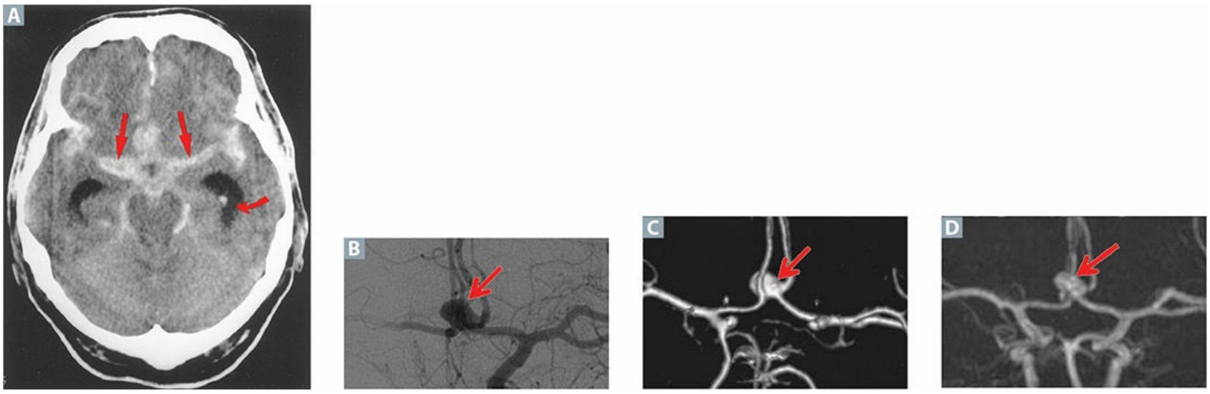


FIGURE 2.9-11. Subarachnoid hemorrhage. Noncontrast CT (A) showing SAH filling the basilar cisterns and sylvian fissures *(straight arrows)*. The *curved arrow* shows the dilated temporal horns of the lateral ventricles/hydrocephalus. Images from a catheter angiogram (B), a CT angiogram (C), and an MRA (D) show a saccular aneurysm arising from the anterior communicating artery *(arrows in B, C, and D)*. (Image A reproduced with permission from Tintinalli JE et al. *Tintinalli’s Emergency Medicine: A Comprehensive Study Guide*. 6th ed. New York, NY: McGraw-Hill; 2004. Images B, C, and D reproduced with permission from Doherty GM. *Current Diagnosis & Treatment: Surgery*. 13th ed. New York, NY: McGraw-Hill; 2010.)

- Lumbar puncture if CT is ⊖ to look for RBCs, xanthochromia (yellowish CSF caused by breakdown of RBCs), ↑ protein (from the RBCs), and ↑ ICP a few hours after onset of thunderclap headache.
- Four-vessel angiography (or equivalent noninvasive angiography such as CTA with three-dimensional reconstructions) once SAH has been confirmed (see Fig. 2.9-11B–D) to

identify source of bleeding. Invasive CTA is warranted in high-risk cases and in those with high clinical suspicion even if CT and LP are unrevealing.

MNEMONIC

Conditions associated with berry aneurysms that can* MAKE *an* SAH *more likely—

Marfan syndrome
Aortic coarctation
Kidney disease (autosomal dominant, polycystic)
Ehlers-Danlos syndrome
Sickle cell anemia; **S**moking tobacco
Atherosclerosis
History (familial); **H**ypertension; **H**yperlipidemia

Treatment

- **Most definitive treatment:** Neurosurgery. May perform angiographic coiling and/or stenting to stabilize aneurysm first.
- Prevention of rebleeding (most dreaded complication and most likely to occur in the first 24 hours) by maintenance of SBP <150 mm Hg until the aneurysm has been coiled or clipped. Choice between coiling and clipping dependent on site of lesion, neck of aneurysm, and availability. Generally, coiling is preferred.
- Prevention of vasospasm (a major cause of delayed morbidity and mortality) and subsequent ischemic stroke (most likely to occur up to 12 days after SAH) by administration of calcium channel blockers (CCBs), such as nimodipine.
- ↓ ICP by raising the head of the bed and instituting hyperventilation in an acute setting (<30 minutes after onset).
- Treatment of hydrocephalus through a lumbar drain, serial LPs, or ventriculoperitoneal shunt.

INTRACEREBRAL HEMORRHAGE

Bleeding within brain parenchyma. Commonly affects deep brain regions such as the basal ganglia, internal capsule, thalamus, pons, and cerebellum. Some risk factors include hypertension, tumor, and illicit drug use. Hypertension is the most common cause of intracerebral hemorrhage, followed by amyloid angiopathy (in older adults).

History/PE

- **Early symptoms/signs:** Focal motor or sensory deficits that often worsen as the hematoma expands
- **Late symptoms/signs:** Features of increased ICP (eg, vomiting and headache, bradycardia, reduced alertness)

Diagnosis

Immediate noncontrast head CT (see Fig. 2.9-12). The physician should look for hyperdense areas, mass effect, or edema that may predict herniation.

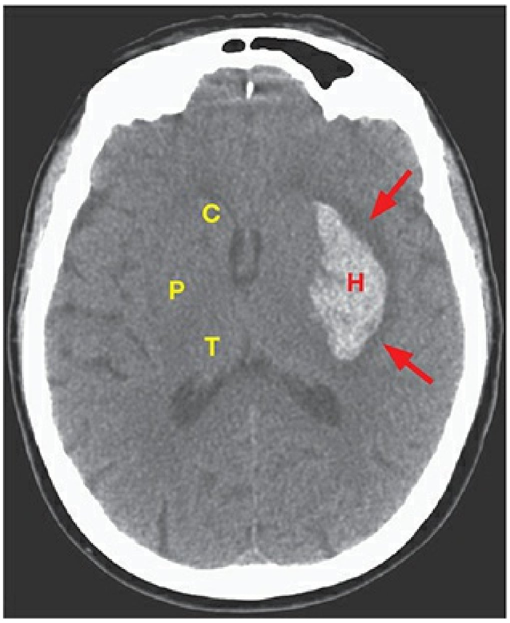


FIGURE 2.9-12. **Intracerebral hemorrhage.** Noncontrast head CT shows an intraparenchymal hemorrhage *(H)* and surrounding edema *(arrows)* centered in the left putamen, a common location for hypertensive hemorrhage. *C*, *P*, and *T* denote the normal contralateral caudate, putamen, and thalamus, respectively. (Reproduced with permission from Fauci AS et al. *Harrison's Principles of Internal Medicine.* 17th ed. New York, NY: McGraw-Hill; 2008.)

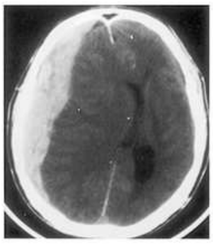
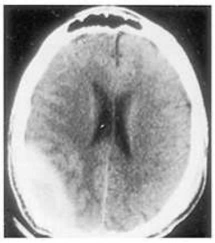
Treatment

- Monitor for signs of rebleed, shift, and possible herniation.
- Suspect herniation if patient develops Cushing triad (hypertension, bradycardia, irregular respirations), fixed pupils, or loss of consciousness.
- Herniation is a medical emergency. Treat initially with mannitol or hypertonic saline in all patients, followed with emergency decompressive craniectomy to allow edema to expand outward.

SUBDURAL AND EPIDURAL HEMORRHAGE

Patients who present after head trauma with headache, focal neurologic deficits, and confusion should always be assumed to have a subdural or epidural hematoma and are in need of urgent neuroimaging. Overall, subdural hematomas are more common in the elderly, whereas epidural hematomas are more common in younger individuals. See Table 2.9-10.

TABLE 2.9-10. **Subdural vs Epidural Hemorrhage**

	ACUTE SUBDURAL	CHRONIC SUBDURAL	EPIDURAL
Common etiology	Head trauma → rupture of bridging veins → accumulation of blood between dura and arachnoid membranes		Head trauma → lateral skull fracture → tear of middle meningeal artery → accumulation of blood between skull and dura mater
Epidemiology	Older adults, patients who overuse alcohol		Severe trauma
History/PE	Within 24 hours with decreased GCS, pupil inequality, and motor deficits	Headache; altered mental status; contralateral hemiparesis; focal neurologic findings; altered mental status in older adults	Immediate loss of consciousness followed by a lucid interval (minutes to hours)
Diagnosis	CT findings: Crescent shaped, concave hyperdensity acutely (isodense subacutely; hypodense chronically) 		CT findings: Lens-shaped, biconvex hyperdensity 
Treatment	Neurosurgical evacuation regardless of symptoms	Neurosurgical evacuation if symptomatic Subdural hematomas that may regress spontaneously	Emergent neurosurgical evacuation Can quickly evolve to brain herniation and death secondary to the arterial source of bleeding
Note	In the setting of mild traumatic brain injury without vomiting, headache, and loss of consciousness and a normal head CT, observe for 4–6 hours. If observation period is unremarkable, the patient can be sent home with extensive return precautions.		

Images reproduced with permission from Aminoff MJ. *Clinical Neurology*, 3rd ed. Stamford, CT: Appleton & Lange; 1996: 296.

KEY FACT

Altered mental status associated with an expanding epidural hematoma occurs within minutes to hours and classically includes acute loss of consciousness → lucid interval → gradual loss of consciousness. With a subdural hematoma, such changes can occur within days to weeks.

CAVERNOUS SINUS THROMBOSIS

The cavernous sinus is a blood-filled collection of venous sinuses on either side of the pituitary gland. Common etiologies involve uncontrolled infections of central facial skin, the orbit, or nasal sinuses that lead to septic thrombosis of the cavernous sinus. *Staphylococcus aureus* is the most common causative agent. Current antimicrobials have greatly ↓ both incidence and mortality. However, this can also occur in the setting of trauma or postsurgery in patients with thrombophilia.

History/PE

- Headache is the most common presenting symptom.
- Patients may present with orbital pain, edema, diplopia, other CN signs secondary to oculomotor, abducens, trigeminal, or trochlear involvement. On examination, they

typically appear ill and have a fever.

- **Late findings:** Altered mental status such as confusion, drowsiness, or coma suggests spread to the CNS or sepsis.

Diagnosis

- MRI (with gadolinium and magnetic resonance [MR] venography) is the main method for diagnosis, but CTA and CT venography are also often used for diagnosis.
- Lab studies show ↑ WBC count.
- Blood cultures reveal the causative agent in up to 50% of cases.

Treatment

- Cavernous sinus thrombosis calls for aggressive and empirical treatment with broad-spectrum antibiotics: vancomycin + third- or fourth-generation cephalosporin (eg, ceftriaxone or cefepime).
- Metronidazole covers anaerobic infection from sinus or dental sources.
- Antifungal therapy is required for fungal cases.
- IV antibiotics are recommended for at least 3 to 4 weeks.
- Anticoagulation with unfractionated heparin or low-molecular-weight heparin may be used to decrease mortality. This may be required for several months.
- Surgical drainage may be necessary if there is no response to antibiotics within 24 hours.

KEY FACT

Procurement of a head CT without contrast before other imaging to evaluate for hemorrhage or structural changes. Imaging should precede LP in light of the risk for herniation.

COMA AND ENCEPHALOPATHY

A state of “unarousable unresponsiveness,” ie, unconsciousness marked by limited to no response to stimuli. Lesser states of impaired arousal are known as “obtundation” or “stupor.” Coma is caused by dysfunction of both cerebral hemispheres or the brainstem (pons or higher), which stems from structural or toxic-metabolic insults.

Common causes may include encephalopathy (hypoxic/ischemic), diffuse axonal injury, brainstem herniation, electrolyte disturbances (eg, hypoglycemia), toxins, and central pontine myelinolysis.

History/PE

- Obtain a complete medical history from witnesses, including current medications (eg, sedatives).
- Conduct thorough medical and neurologic examinations, including assessments of mental status, spontaneous motor activity, muscle tone, breathing pattern, fundoscopy (to look for papilledema), pupillary resting diameters and responses to light response, eye movements, corneal reflex, gag reflex, and motor or autonomic responses to noxious stimuli applied to the limbs, trunk, and face (eg, retromandibular pressure, nasal tickle).

Diagnosis

Typically made by a combination of the history/physical examination and laboratory tests or neuroimaging:

- **Best initial step:** Check of glucose, electrolytes, calcium; procurement of renal panel, liver function tests (LFTs), arterial blood gases (ABGs), a toxicology screen, and blood and CSF cultures.
- **Next step:** Vital signs, ventilatory pattern, neurologic examination. The physician can identify treatable conditions such as infection, metabolic conditions, seizures, intoxications/overdose, and surgical lesions.
- **Test of choice:** CT head. MRI is superior for encephalitis, early strokes, diffuse axonal injury (DAI), and multiple small hemorrhages. LP and electroencephalography (EEG) should also be part of the diagnostic workup when neuroimaging and metabolic studies have not disclosed the etiology.
- Procurement of an MRI to exclude structural changes and ischemia (eg, brainstem).

Q 1

A 68-year-old man presents to the emergency department with numbness and droop on the right side of the face, inability to speak, and numbness and weakness in the right arm that began 2 hours ago. Where is this lesion, and what is the next best step in management?

Q 2

A 59-year-old man with prior medical history of polycystic kidney disease was admitted for treatment of SAH. Four days after admission, he developed weakness in his right arm. What could have prevented this?

Q 3

A 59-year-old man with prior medical history of polycystic kidney disease is admitted for treatment of SAH. Four hours after admission, he develops weakness in his left arm. What is the cause of this new finding?

- Rule out catatonia, conversion unresponsiveness, “locked-in” syndrome, or persistent vegetative state (PVS), all of which can be confused with true coma (see Table 2.9-11).

TABLE 2.9-11. **Differential Diagnosis of Minimally Conscious State**

VARIABLE	"LOCKED-IN" SYNDROME	PERSISTENT VEGETATIVE STATE	COMA	BRAIN DEATH
Alertness	Wakeful and aware with retained cognitive abilities	Awake but not aware; eyes open and closed—sleep-wake cycles present	Unconscious, eyes closed; no sleep-wake cycles	Unconscious; no sleep-wake cycles
Most common causes	Central pontinemyelinolysis (after rapid sodium correction), brainstem stroke, advanced ALS	Diffuse cortical injury or hypoxic ischemic injury	Diffuse hypoxic encephalopathy, widespread infection, electrolyte disturbances, toxins	Same as coma
Voluntary motor ability	Eyes and eyelids	None	None	None
Respiratory drive	Yes	Yes	Yes	None

KEY FACT

Artificial life support can be discontinued only after two physicians have declared the patient legally brain dead.

Treatment

Initial treatment should consist of the following measures:

- **Stabilize the patient:** Attend to **ABCs.**
- **Reverse the reversible:** Administer **DONT—D**extrose, **O**xygen, **N**aloxone, and **T**hiamine.
- Identify and treat the underlying cause and associated complications.
- Prevent further damage.

1 A

Occlusion of the left middle cerebral artery (MCA) is suspected, as aphasia and contralateral sensory loss and weakness are part of the description. CT of brain without contrast should be done to rule out hemorrhage and assess whether tPA should be initiated.

2 A

This patient's focal weakness is probably caused by ischemia secondary to vasospasm, so nimodipine administration could prevent this adverse event.

3 A

New onset of neurologic symptoms within 24 hours following an SAH is most likely caused by rebleeding of the aneurysm (as opposed to ischemia days after, which is caused by vasospasm).

APHASIA

A general term for speech and language disorders. Usually results from lesions (eg, strokes, tumors, abscesses) in the "dominant hemisphere." The left hemisphere is dominant in >95% of right-handed people and in 60% to 80% of left-handed people.

BROCA/EXPRESSIVE APHASIA

A disorder of spoken and/or written language production with intact comprehension. Caused by an insult to the Broca area in the posterior inferior frontal cortex (see Fig. 2.9-13). Often secondary to a left superior middle cerebral artery (MCA) stroke. Also known as *motor aphasia*.

History/PE

Presents with impaired speech production, frustration with awareness of deficits, arm and facial hemiparesis, hemisensory loss, and apraxia of the oral muscles. Speech is described as "telegraphic" with few words and frequent pauses.

KEY FACT

Broca aphasia = motor aphasia, expressive aphasia, or nonfluent aphasia
Wernicke aphasia = sensory aphasia, receptive aphasia, or fluent aphasia

Treatment

Speech therapy (varying outcomes with intermediate prognosis).

KEY FACT

In true Broca and Wernicke aphasia, repetition is impaired. If repetition is intact, the deficit is called transcortical motor aphasia (TMA) or transcortical sensory aphasia (TSA), and it is caused by a lesion around either the Broca area or the Wernicke area, respectively. Also called secondary aphasia.

WERNICKE/RECEPTIVE APHASIA

A disorder of language comprehension with intact yet nonsensical production. Caused by an insult to the Wernicke area in the left posterior superior temporal (perisylvian) lobe. Often secondary to left inferior/posterior MCA embolic stroke (see Fig. 2.9-13).

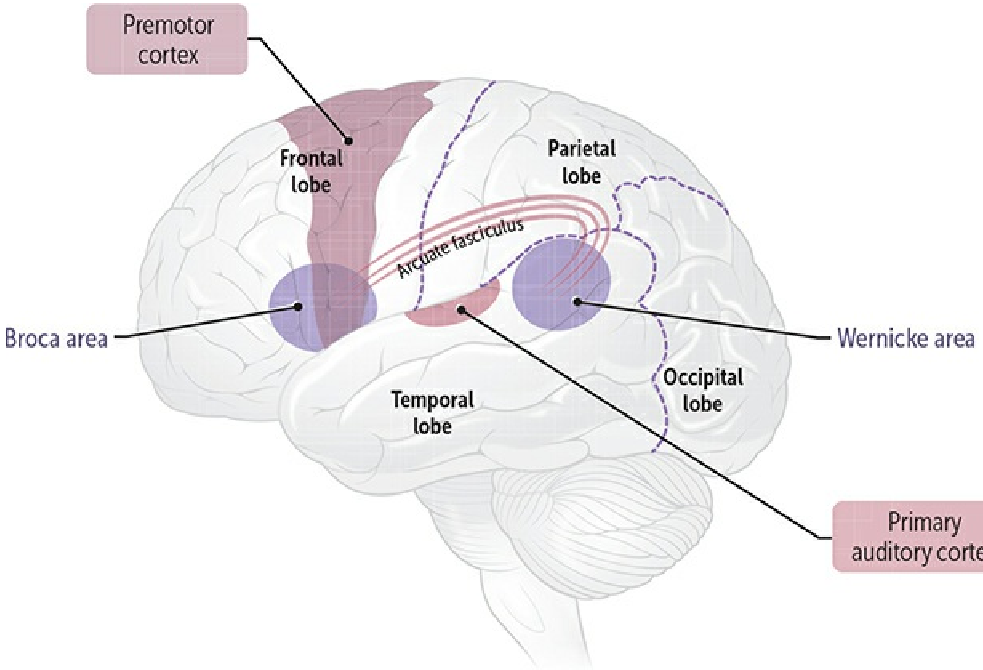

Premotor cortex
Frontal lobe
Parietal lobe
Arcuate fasciculus
Broca area
Wernicke area
Temporal lobe
Occipital lobe
Primary auditory cortex

FIGURE 2.9-13. **Cerebral cortex with Broca and Wernicke areas highlighted.** (Reproduced with permission from USMLE-Rx.com.)

- ***Hx/PE:*** Presents with preserved fluency of language with impaired repetition and comprehension, leading to "word salad." Patients are unable to follow commands, make frequent use of neologisms (made-up words) and paraphasic errors (word substitutions), and show lack of awareness of deficits (see Fig. 2.9-14).

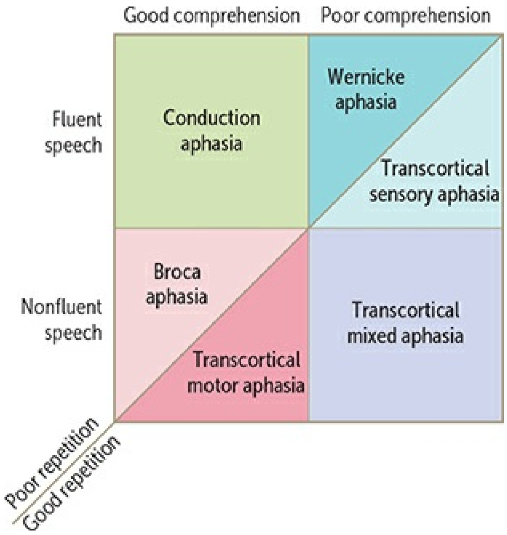

Good comprehension
Poor comprehension
Fluent speech
Nonfluent speech
Conduction aphasia
Wernicke aphasia
Transcortical sensory aphasia
Broca aphasia
Transcortical motor aphasia
Transcortical mixed aphasia
Poor repetition
Good repetition

FIGURE 2.9-14. **Aphasia classification.** (Reproduced with permission from USMLE-Rx.com.)

- ***Tx:*** Treatment of underlying etiology and institution of speech therapy.

MNEMONIC

BROca is **BRO**ken and **W**ernicke is **W**ordy.

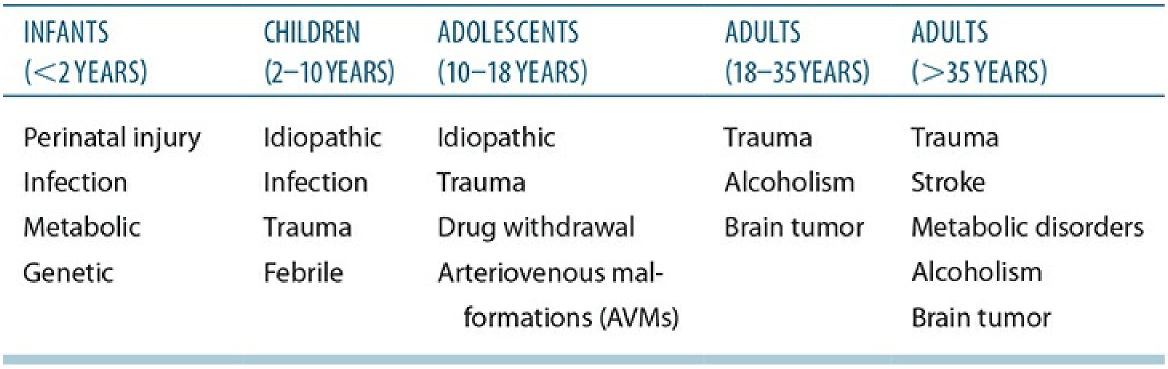
Q

An 82-year-old woman presents to the emergency department with a 2-day history of difficulty speaking and weakness in her right face and arm. During the interview, she speaks in two- to three-word choppy sentences and can follow commands. She cannot repeat what you say. Where is her lesion?

SEIZURE DISORDERS

Sudden changes in neurologic activity caused by abnormal electrical activity in the brain that can often be detected on EEG. See Table 2.9-12 for common etiologies by age. Etiologies of seizures, and their distinguishing features, include the following:

TABLE 2.9-12. Causes of Seizure by Age Group



INFANTS (<2 YEARS)	CHILDREN (2–10 YEARS)	ADOLESCENTS (10–18 YEARS)	ADULTS (18–35 YEARS)	ADULTS (>35 YEARS)
Perinatal injury	Idiopathic	Idiopathic	Trauma	Trauma
Infection	Infection	Trauma	Alcoholism	Stroke
Metabolic	Trauma	Drug withdrawal	Brain tumor	Metabolic disorders
Genetic	Febrile	Arteriovenous malformations (AVMs)		Alcoholism
				Brain tumor

- **Idiopathic epilepsy (recurrent, unprovoked seizures):** May be caused by genetics, developmental factors, early life brain injuries, and so on.
- **Causes of acquired epilepsy:**
  - **Structural brain lesion (tumor, stroke, AVM hemorrhage, or developmental abnormality):** tend to have focal onset or focal postictal deficit, suggesting focal CNS pathology.
  - **Nonneurologic etiologies (ie, provoked seizures):** Hypoglycemia, hyponatremia, hypocalcemia, hyperosmolar states, hepatic encephalopathy, uremia, porphyria, drug overdose (cocaine, antidepressants, neuroleptics, methylxanthines, lidocaine), drug withdrawal (alcohol and other sedatives), eclampsia, hyperthermia, hypertensive encephalopathy, head trauma, and cerebral hypoperfusion.

CLASSIFICATION OF SEIZURE

A seizure is classified as partial (focal) or generalized (see Fig. 2.9-15).

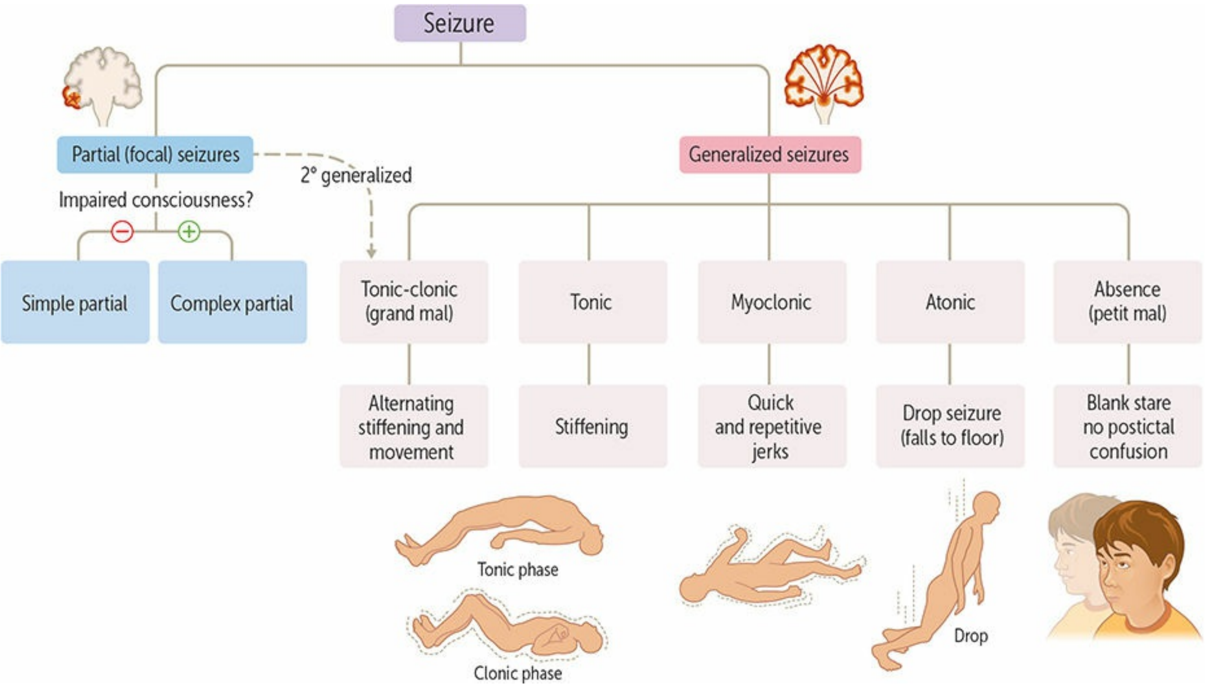

Seizure
Partial (focal) seizures
2° generalized
Generalized seizures
Impaired consciousness?
Simple partial
Complex partial
Tonic-clonic (grand mal)
Tonic
Myoclonic
Atonic
Absence (petit mal)
Alternating stiffening and movement
Stiffening
Quick and repetitive jerks
Drop seizure (falls to floor)
Blank stare no postictal confusion
Tonic phase
Clonic phase
Drop

FIGURE 2.9-15. **Classification of seizures.** (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

Both simple partial and complex partial seizures may evolve into secondary generalized seizures.

KEY FACT

Focal seizures can change into bilateral tonic-clonic type and may have associated loss of consciousness and postictal confusion.

KEY FACT

If an adult patient presents with an episode of lip smacking associated with an impaired level of consciousness and followed by confusion, think complex partial seizures.

KEY FACT

If a patient presents with uncontrollable twitching of their thumb and is fully aware of their symptoms, think simple partial seizures.

KEY FACT

If a patient presents with clonic movements associated with loss of consciousness and incontinence, think tonic-clonic (grand mal) seizures.

History/PE

- **Focal (partial):** Abnormal electrical activity arises from a discrete region (or multiple discrete regions) of the brain. It can involve motor, sensory, autonomic, or psychic features (eg, fear, déjà vu, hallucinations). Aura is common (auditory, visual, olfactory, or tactile hallucinations). Automatisms like lip smacking, picking, and swallowing are common. A postictal focal neurologic deficit (eg, hemiplegia/hemiparesis, or Todd paralysis) is possible and usually resolves within 24 hours. It can be simple or complex.
  - **Aware:** Previously called simple partial seizures. No impaired level of consciousness.
  - **Impaired awareness:** Previously called complex partial seizures. Typically start on one side of the brain, often involving the temporal lobe (70%–80%) with bilateral spread of the aberrant electrical discharge, leading to impaired level of consciousness. Postictal confusion, disorientation, and amnesia are characteristic.
- **Generalized seizure:** Seizure activity that involves both cerebral hemispheres, resulting in impaired level of consciousness. Classified as motor (tonic-clonic, other motor) or nonmotor (absence) type.
- **Tonic-clonic seizure:** Sudden loss of consciousness with extension of the back and contraction of muscles (chest and extremities); repetitive, symmetric clonic (alternation between muscle contraction and relaxation) movements. Etiology often idiopathic. Simple and complex partial seizures may evolve into secondary generalized tonic-clonic seizures.
  - Marked by incontinence and tongue biting.
  - Patients may appear cyanotic during the ictal period.
  - Postictal confusion and drowsiness. Muscle aches and headaches may also be present.
- **Absence seizure:** A form of generalized seizure. Presents with brief (5- to 10-second), often unnoticeable episodes of impaired consciousness (petit mal seizures) occurring up to hundreds of times per day. Patient can appear to be daydreaming or staring. Symptoms may include sudden stops in motion, lip smacking, eyelid fluttering, and chewing motions. It can be triggered by hyperventilation. There is no postictal phase. Absence seizure begins in childhood and subsides before adulthood. It is often familial.
- **Unknown seizure:** Generalized or focal. Often the beginning of seizure is not clear.

A

This patient presents with Broca or expressive aphasia. In Broca aphasia, the lesion is in the posterior frontal cortex of the dominant side of the brain. In this case, the lesion also involves the face and arm regions of the motor cortex, which are immediately adjacent to Broca area on the left hemisphere.

Diagnosis

- Clinical history by a bystander and physical examination are always clues to the diagnosis and differentiation among similarly appearing clinical symptoms. The history should look for brain trauma, infection, neoplasm, stroke, or developmental issues.
- **Best initial step:** EEG. Brain MRI is considered for focal seizures.
- **Focal seizure:** Search for epileptogenic focus (CT or contrast MRI).
- **Absence seizure:** EEG shows three-per-second spike-and-wave discharges (remember classic EEG findings, but do not worry about learning how to read them!). EEG changes can be triggered by hyperventilation.
- **Tonic-clonic seizure:** EEG typically shows 10-Hz activity during the tonic phase and slow waves during the clonic phase (normal = pseudoseizures).

- Serum prolactin levels may be elevated in the immediate postictal period of generalized and complex-partial seizures (vs pseudoseizures).
- **To rule out:** Systemic causes with a CBC, electrolytes, calcium, fasting glucose, LFTs, a renal panel, ESR, and a toxicology screen.

Treatment

- Secure airway when appropriate.
- For acute seizures lasting longer than 5 minutes, see treatment of status epilepticus later in chapter.
- In cases of systemic secondary seizures, treat the underlying cause (eg, low blood sugar, alcohol withdrawal, or fever in children).
- Anticonvulsants for partial and tonic-clonic seizures: levetiracetam, phenytoin, carbamazepine, and valproic acid have similar efficacy and can be used as chronic monotherapy.
- In children, levetiracetam is the first-line anticonvulsant. If fever is present, treat fever but also give lorazepam.
- If a certain antiepileptic is ineffective as monotherapy, try an alternative. If the alternative is ineffective, try a regimen of multiple antiepileptics.
- Other treatment options include gabapentin, topiramate, and oxcarbazepine.
- **Absence seizure:** First-line is ethosuximide; second-line is valproic acid.

Q

A 40-year-old man presents to the emergency department with a single simple partial seizure of 1 minute but is no longer symptomatic. He also complains of 2 months of morning headaches and one episode of vomiting in the past week. What is the next step in management?

- **Intractable temporal lobe seizure:** Consider anterior temporal lobectomy (epilepsy surgery) and/or vagal nerve stimulator.
- Treatment is not necessary for a single episode of seizure.

STATUS EPILEPTICUS

A **medical emergency** consisting of prolonged seizures (usually >5 minutes) or two or more seizures that occur without a return to baseline consciousness within 30 minutes or continuous clinical and/or electrographic seizure activity

- Common causes include anticonvulsant withdrawal/noncompliance, anoxic brain injury, EtOH/sedative withdrawal or other drug intoxication, and metabolic disturbances (eg, hyponatremia), head trauma, and infection.
- Mortality is 10% to 20%.

Diagnosis

- Treatment and diagnostic workup should be initiated simultaneously.
- Determination of the underlying cause should entail collateral history, physical exam, CBC, electrolytes, calcium, glucose, ABGs, LFTs, BUN/creatinine, ESR, antiepileptic drug levels, and a toxicology screen.

- Continuous EEG monitoring is indicated if nonconvulsive status epilepticus is suspected or if patient is not waking up after clinically obvious seizures stop.
- If intracranial pathology is suspected, the physician should obtain a stat head CT.
- An LP should be procured in the setting of fever or meningeal signs, but only after a CT scan has been obtained to assess the safety of the LP.

KEY FACT

Although status epilepticus is traditionally defined as seizures lasting >5 minutes, treatment should begin for any seizure lasting >5 minutes to prevent brain-induced cardiac, pulmonary, and other complications.

Treatment

- **Best initial step:** Like in all emergencies, treatment starts with the ABCs. During the stabilization phase, the following interventions usually occur simultaneously:
  - Stabilization of the airway for breathing and circulation
  - Check of oxygen saturation and use of supplemental oxygen or consideration of intubation
  - Connection of ECG monitor
  - Determination of capillary blood glucose reading and treatment if it is less than 60 mg/dL
  - Procurement of IV access to collect blood for electrolytes, hematologic workup, toxicology screen, and anticonvulsant levels (if already on medications)
- **Best initial therapy:** Benzodiazepines are given intravascularly: IV lorazepam or IV diazepam. These steps (from ABCs to IV benzodiazepines) are carried out between 5 and 20 minutes of resuscitation:
  - This is given if the seizure persists after 5 minutes (ie, the stabilization phase) or recurs when the patient is being treated.
  - Alternatives include phenobarbital, rectal diazepam for children, and intranasal midazolam.
- **Next step in management:** If seizure persists despite these treatments, the physician should consider IV fosphenytoin, IV valproic acid, or IV levetiracetam.
- Last-resort options include repetition of second-line drugs or induction of coma by use of general anesthetics (eg, propofol).

MNEMONIC

Withdrawal from ABBA can cause seizures—

Alcohol
Benzodiazepines
Barbiturates
Anticonvulsants

The next step in management is to order a CT of the brain because the history is suggestive of a brain tumor and the patient is no longer symptomatic. If seizures recur, consider beginning anticonvulsant therapy.

VERTIGO

Before discussing conditions that cause vertigo, it is worth defining vertigo and differentiating it from lightheadedness. “Dizziness” is often used to describe vertigo and lightheadedness. Vertigo feels as if one or one’s surroundings are moving when there is no actual movement. Lightheadedness feels as if one is about to faint or “pass out.” Conscious sensation of vertigo occurs in the cerebral cortex as a result of an error signal of observed over expected from the vestibular apparatus in the inner ear and brainstem, or in response to imbalances in vestibular input between left and right sides.

Vertigo can be divided into central and peripheral vertigo. Central vertigo is caused by lesions in the CNS. Common characteristics include severe postural and gait instability, purely vertical or purely torsional nystagmus, and other focal neurologic signs. Peripheral vertigo is caused by lesions in the inner ear. Common characteristics include deafness, tinnitus, horizontal torsional nystagmus, and absent focal neurologic signs.

BENIGN PAROXYSMAL POSITIONAL VERTIGO

A common cause of recurrent peripheral vertigo resulting from displacement of otoliths (“ear stones”), which lead to disturbances in the semicircular canals—the parts of the ear responsible for detecting head rotation. The posterior canal is the most common site.

History/PE

Patients present with transient, episodic vertigo (lasting <1 minute) and nystagmus triggered by changes in head position (eg, while turning in bed, getting in and out of bed, or reaching overhead). Benign paroxysmal positional vertigo (BPPV) may be accompanied by nausea and vomiting.

KEY FACT

Progressive bilateral (high-frequency) sensorineural hearing loss and occasional tinnitus are normal (presbycusis). They are typically noticed by 60 years of age.

Diagnosis

- **Dix-Hallpike maneuver** (used primarily to identify posterior canal BPPV): The patient should turn their head 45 degrees right or left and go from a sitting to a supine position. If vertigo and the typical nystagmus (rotatory nystagmus with the fast phase toward the affected side) are reproduced, BPPV is the likely diagnosis. If positive, the test should be repeated. In BPPV, the vertigo fatigues with the second attempt due to washout of the otoconia.
- Nystagmus that persists for >1 minute, is not suppressed by visual fixation, and lacks fatigability along with gait disturbance should raise concern for a central lesion.

Treatment

- Epley maneuver (an extended version of the Dix-Hallpike maneuver used as treatment) resolves 85% of cases.
- BPPV usually subsides spontaneously in weeks to months, but up to 30% recur within 1 to 3 years. Long-term use of antivertigo medications (eg, meclizine) are generally contraindicated, as they have limited efficacy, they are sedating, and they inhibit vestibular compensation, which may lead to chronic unsteadiness.

ACUTE PERIPHERAL VESTIBULOPATHY (LABYRINTHITIS OR VESTIBULAR NEURITIS)

History/PE

- Presents with acute onset of severe vertigo, head motion intolerance, and gait unsteadiness accompanied by nausea, vomiting, and nystagmus. Often preceded by viral infection.
- **Labyrinthitis:** Inflammation of the labyrinth, which contains organs of both hearing and equilibrium. Auditory or aural symptoms (tinnitus, ear fullness, or **hearing loss**) present. Lateral pontine/cerebellar stroke (anterior inferior cerebellar artery territory) may present with similar symptoms but may have additional occipital headache, ataxia, nystagmus, and somatosensory deficits (supplies spinal tract of CN V and spinothalamic tract).
- **Vestibular neuritis:** Inflammation of the vestibular nerve, responsible for balance and equilibrium. Lacks auditory or aural symptoms. Lateral medullary/cerebellar stroke (posterior inferior cerebellar artery territory) can present with similar symptoms, but patients have focal findings on exam (ie, ataxia, sensory loss, dysphagia, Horner syndrome).

KEY FACT

If a patient complains of vertigo and vomiting without hearing loss for 1 week after having been diagnosed with a viral infection, think acute vestibular neuritis.

Diagnosis

- A diagnosis of exclusion once the more serious causes of vertigo (eg, cerebellar/brainstem stroke) have been ruled out. Acute peripheral vestibulopathy presents with vertigo over minutes to hours, but the onset of vertigo due to a vascular event is more hyperacute.
- Acute peripheral vestibulopathy demonstrates the following:
  - An abnormal vestibulo-ocular reflex, as determined by a bedside head impulse test (ie, patient not able to maintain visual fixation during rapid head rotation toward side of the lesion, followed by a compensatory saccade once the head stops moving)
  - A predominantly horizontal nystagmus that always beats in one direction, towards the opposite side of the lesion
  - No vertical eye misalignment by alternate cover testing
- If patients are "high risk" (ie, atypical eye findings or neurologic symptoms or signs; cannot stand independently; have a new-onset headache, head, or neck pain; are >50 years of age; or have one or more stroke risk factors), MRI with diffusion-weighted imaging and MRA are indicated.

Treatment

Acute treatment consists of corticosteroids given <72 hours after symptom onset, antivertigo agents (eg, meclizine), and antiemetics. The condition usually subsides spontaneously within weeks to months.

MÉNIÈRE DISEASE

A cause of recurrent vertigo with unilateral auditory symptoms that affects at least 1 in 500 individuals in the United States. More common among women. This disorder of the inner ear is characterized by ↑ volume of endolymph (endolymphatic hydrops).

History/PE

Presents with the classic tetrad of episodic vertigo, tinnitus, aural fullness, and hearing loss. Episodes often last minutes to hours. Nausea and vomiting are typical. Patients progressively lose low-frequency hearing over years and may become deaf on the affected side.

Diagnosis

Usually clinical. Based on the following:

- Two episodes lasting ≥20 minutes with remission of symptoms between episodes
- Hearing loss documented at least once with audiometry
- Tinnitus or aural fullness

MRI of the temporal bone often helpful to rule out other causes that present similarly (eg, tumors, aneurysms, multiple sclerosis)

Treatment

- **Acute:** Meclizine or benzodiazepines to control spinning sensation during acute attacks; antiemetics for nausea/vomiting.
- **Chronic:** Dietary/lifestyle changes that limit salt, caffeine, nicotine, and alcohol intake to avoid fluid retention. Betahistine (vasodilator that improves circulation in the inner ear) or diuretics can be used for patients with refractory symptoms not amenable to lifestyle changes.
- For severe unilateral cases, intratympanic injection of gentamicin into the middle ear (absorbed by the inner ear) is shown to reduce the frequency and severity of vertigo attacks.

KEY FACT

The incidence of *Haemophilus influenzae* type B meningitis has greatly ↓ over the past 10 to 15 years as a result of routine vaccination.

KEY FACT

A petechial or purpuric rash is characteristic of meningococcal meningitis. Waterhouse-Friderichsen syndrome (acute adrenal insufficiency caused by adrenal gland hemorrhage) is characterized by profound hypotension and has a high mortality.

CNS INFECTIONS

MENINGITIS

Acute bacterial meningitis is a life-threatening emergency. Viral (also called "aseptic") meningitis is more common and clinically less morbid. Risk factors for meningitis include recent ear infection, sinusitis, immunodeficiencies, recent neurosurgical procedures, crowded living conditions (ie, college dorms, military), and sick contacts. Commonly encountered causative organisms are listed in Table 2.9-13.

TABLE 2.9-13. Common Pathogens Causing Meningitis

BACTERIAL	VIRAL (ASEPTIC)	HIV
Streptococcus pneumoniae (#1 in adults) *Neisseria meningitidis* (#1 in teens) Group B Streptococcus (GBS) and *Escherichia coli* (in neonates) *Haemophilus influenzae* serotype b, *Listeria* (see Fig. 2.9-16)	Enteroviruses: ▪ Echovirus ▪ Coxsackie ▪ HSV-2	*Cryptococcus neoformans,* cytomegalovirus (CMV), HSV, varicella zoster virus (VZV), tuberculosis (TB), toxoplasmosis, and John Cunningham (JC) virus (progressive multifocal leukoencephalopathy [PML])

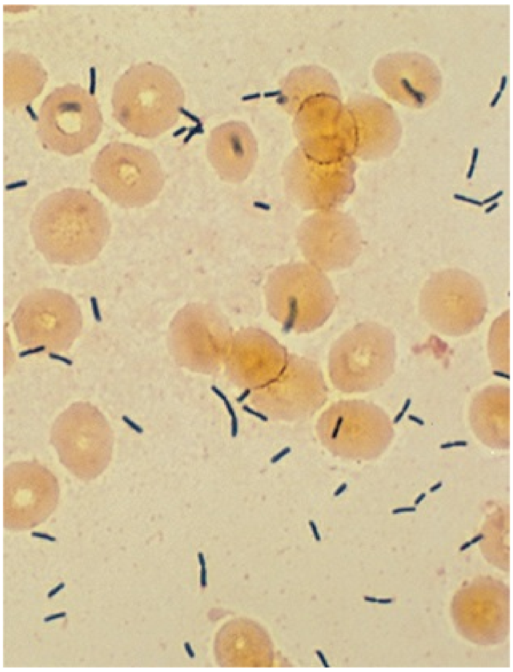


FIGURE 2.9-16. **Listeria.** These numerous gram-positive, rod-shaped bacilli were isolated from the blood of a patient with *Listeria* meningitis. (Reproduced with permission from USMLE-Rx.com.)

History/PE

- Classic triad of fever, headache, and neck stiffness in one half of patients

- Other symptoms include malaise, photophobia, altered mental status, nausea/vomiting, seizures, or signs of meningeal irritation (⊕ Kernig [thigh flexion → pain/resistance with knee extension] and Brudzinski [neck flexion → knee and hip flexion] signs).

Diagnosis

- **Best initial test:** An LP for CSF analysis, Gram stain, and culture, ideally before initiation of antibiotics and procurement of glucose, protein, WBC count plus differential, RBC count, and opening pressure (in the absence of papilledema or focal neurologic deficits) information.
- Viral polymerase chain reactions ([PCRs]; eg, herpes simplex virus [HSV]); cryptococcal antigen (for HIV patients).
- CT or MRI indicated in a minority of patients before LP, in particular those with altered mental status, papilledema, or focal neurologic deficits to exclude a mass lesion or ↑ ICP. If CT is being obtained, empiric antibiotics should be started beforehand. Obtain blood cultures. CBC may reveal leukocytosis. CSF findings vary (see Table 2.9-14).

TABLE 2.9-14. **CSF Profiles**

	RBCS (PER MM^3)	WBCS (PER MM^3)	GLUCOSE (MG/DL)	PROTEIN (MG/DL)	OPENING PRESSURE (CM H_2O)	APPEARANCE	GAMMA GLOBULIN (% PROTEIN)
Normal	<10	<5	>2/3 of serum	15–45	10-20	Clear	3–12
Bacterial meningitis	↔	↑ (>1000 polymorphonuclear [PMN] cells)	↓	↑↑	↑	Cloudy/purulent	↔ or ↑
Viral/aseptic meningitis	↔	↑ (monos/lymphs)	↔	↔ or ↑	↔ or ↑	Most often clear	↔ or ↑
Subarachnoid hemorrhage	↑↑	↑	↔	↑	↔ or ↑	Yellow/red	↔ or ↑
Guillain-Barré syndrome	↔	↔	↔ or ↑	↑↑	↔	Clear or yellow (high protein)	↔
Multiple sclerosis	↔	↔ or ↑	↔	↔	↔	Clear	↑↑
Idiopathic intracranial hypertension	↔	↔	↔	↔	↑↑↑	Clear	↔

Treatment

- **Most accurate treatment:** Rapid administration of antibiotics for bacterial meningitis (see Table 2.9-15).

TABLE 2.9-15. **Empiric Treatment of Bacterial Meningitis**

AGE	CAUSATIVE ORGANISM	TREATMENT
<1 month	GBS, *E coli*/gram ⊖ bacilli, *Listeria*	Ampicillin + cefotaxime or gentamicin
1–3 months	*S pneumoniae, N meningitidis, H influenzae type b*	Vancomycin IV + ceftriaxone or cefotaxime
3 months to adulthood	*N meningitidis, S pneumoniae*	Vancomycin IV + ceftriaxone or cefotaxime
>50 years/alcohol use disorder/chronic illness/ immunocompromise	*S pneumoniae*, gram ⊖ bacilli, *Listeria, N meningitidis*	Ampicillin + vancomycin + cefotaxime or ceftriaxone

- Most cases of viral meningitis can be treated with supportive care and close follow-up.
- Close contacts of patients with meningococcal meningitis should receive rifampin or ceftriaxone (preferred during pregnancy) or ciprofloxacin (avoid for those pregnant or <18 years of age) and the meningococcal vaccine.
- Dexamethasone ↓ mortality, hearing loss, and short-term neurologic complications in bacterial meningitis caused by *S pneumoniae* in adults, if given 15 to 20 minutes before antibiotics and ↓ hearing loss in children, particularly those with *H influenzae* type b (Hib) meningitis.
- If immunocompromised, >50 years of age, or neonate, add ampicillin for *Listeria*.

Complications

Sensorineural hearing loss, mental impairment, seizures, cerebral edema, ↑ ICP, brain abscess, ventriculitis/hydrocephalus, focal neurologic deficits (eg, cranial nerve palsies), hyponatremia, coma, and death.

CRYPTOCOCCAL MENINGITIS

- **Risk factors:** AIDS, exposure to pigeon droppings
- ***Hx/PE:*** Subacute onset of headache, fever, impaired mentation, signs of increased ICP, and absent meningeal signs. The differential diagnosis includes toxoplasmosis, lymphoma, tuberculosis (TB) meningitis, AIDS dementia complex, progressive multifocal leukoencephalopathy (PML), HSV encephalitis, and other fungal disease.
- ***Dx:*** LP (↓ CSF glucose, ↑ protein, ↑ leukocyte count with monocytic predominance, ↑↑ opening pressure), ⊕ cryptococcal antigen testing in CSF and/or blood, CSF India ink stain, and fungal culture.
- ***Tx:***
  - **Induction phase:** Amphotericin B (IV) + flucytosine (PO) for ≥2 weeks
  - **Consolidation phase:** Fluconazole (PO) for ≥8 weeks
  - **Maintenance phase:** Fluconazole ≥1 year; can thereafter discontinue if on antiretroviral therapy (ART) with CD4+ cell count >100/mm^3 and viral load undetectable for >3 months
- ↑ opening pressure may require serial LPs or a ventriculoperitoneal shunt for management.

KEY FACT

The CSF antigen test for cryptococcal meningitis is highly sensitive and specific.

Q

A 19-year-old college student is brought to the emergency department from her dorm room, where she was found by her roommate in a confused state. She complains of fever, nausea, vomiting, and pain in her neck and head. She has a petechial rash on her legs. CSF examination reveals a glucose level of 22 mg/dL, a protein level of 140 mg/dL, and a WBC count of 1400/mm^3. What is the most likely organism responsible for her condition?

TOXOPLASMOSIS

Risk factors include ingesting raw or undercooked meat, eating contaminated fruits or vegetables, exposure to cat feces, and drinking unpasteurized milk.

History/PE

- Primary infection is usually asymptomatic.
- Reactivated toxoplasmosis occurs in immunosuppressed patients and may present in specific organs (brain, lung, and eye > heart, skin, gastrointestinal [GI] tract, and liver).
- Encephalitis is common in seropositive AIDS patients. Classically, CNS lesions present with fever, headache, altered mental status, seizures, and focal neurologic deficits.

Diagnosis

- Serology, PCR (indicates exposure and risk for reactivation), and occasionally tissue exam for histology.
- In the setting of CNS involvement, CT scan (toxoplasmosis indicated by multiple isodense or hypodense ring-enhancing mass lesions) or an MRI (has a predilection for the basal ganglia; more sensitive).

Treatment

- **Most accurate treatment:** Induction with high-dose PO pyrimethamine + sulfadiazine and leucovorin (a folic acid analog to prevent hematologic toxicity) for 4 to 8 weeks; maintenance with a low-dose regimen until the disease has resolved clinically and radiographically
- Use of trimethoprim-sulfamethoxazole ([TMP-SMX], eg, Bactrim DS) or pyrimethamine + dapsone for prophylaxis in patients with a CD4+ cell count <100/mm^3 and a ⊕ toxoplasmosis IgG

KEY FACT

Ring-enhancing lesions in patients with AIDS should always prompt consideration of toxoplasmosis and CNS lymphoma.

KEY FACT

The presence of RBCs in CSF (pink-colored CSF) without a history of trauma is highly suggestive of HSV encephalitis.

ENCEPHALITIS

HSV and arboviruses are the most common causes of encephalitis. Rarer etiologies include CMV, toxoplasmosis, West Nile virus, varicella zoster virus (VZV), *Borrelia*, *Rickettsia*, *Legionella*, enterovirus, *Mycoplasma*, and cerebral malaria. Children and older adults are the most vulnerable.

History/PE

- Altered consciousness, headache, fever, seizures.
- Lethargy, confusion, coma, focal neurological deficits may also be present.
- Differentials include brain abscess, malignancy, SDH, SAH, toxic-metabolic encephalopathy.

KEY FACT

CNS infections key words:
Photophobia, nuchal rigidity = meningitis
Focal neurologic deficits = brain abscess
Confusion, altered mental status = encephalitis

Diagnosis

- The physician should procure a CT immediately to rule out other life-threatening conditions that cause neurologic symptoms and may demonstrate characteristic temporal lobe signal abnormalities in HSV encephalitis (see Fig. 2.9-17).

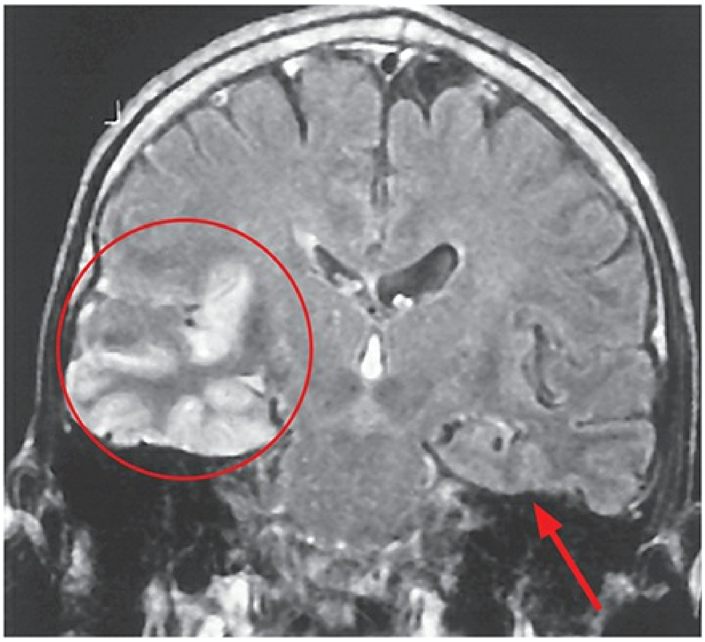


FIGURE 2.9-17. **HSV encephalitis.** Coronal fluid-attenuated inversion recovery (FLAIR) image of a young man with HSV encephalitis shows the characteristic MRI pattern within the cortex of the right temporal lobe *(circle)*. The left temporal lobe is also involved *(arrow)*, but to a lesser extent. (Reproduced with permission from Fauci AS et al. *Harrison's Principles of Internal Medicine*, 17th ed. New York, NY: McGraw-Hill; 2008.)

- CSF shows lymphocytic pleocytosis and moderately ↑ protein. The glucose level is low in tuberculous, fungal, bacterial, and amebic infections.
- Perform CSF Gram stain (bacteria); acid-fast stain (mycobacteria); India ink stain (*Cryptococcus*); cultures for all organism types; and PCR for HSV, cytomegalovirus (CMV), Epstein-Barr virus (EBV), VZV, and enterovirus. Obtain West Nile IgM serologies and consider a wet preparation (free-living amebae) and a Giemsa stain (trypanosomes) if the history is suggestive.

A

Neisseria meningitidis is the most likely organism responsible for her condition. The physician should suspect meningococcal meningitis in a very ill patient with fever, headache, altered mental status, a petechial rash in the lower extremities, and a CSF profile indicative of bacterial meningitis.

Treatment

- **HSV encephalitis:** Immediate IV acyclovir, foscarnet if resistant
- **CMV encephalitis:** IV ganciclovir ± foscarnet
- **Suspected Rocky Mountain spotted fever or ehrlichiosis:** Doxycycline
- **Lyme encephalitis:** Ceftriaxone

BRAIN ABSCESS

A focal suppurative infection of the brain parenchyma, usually with a "ring-enhancing" appearance caused by a fibrous capsule (see Fig. 2.9-18). The most common pathogens are *Streptococci, Staphylococci,* and anaerobes; 80% to 90% are polymicrobial. Nonbacterial causes include *Toxoplasma* and *Candida; Aspergillus* and zygomycosis should be considered in immunocompromised hosts, and neurocysticercosis should be considered in relevant epidemiologic settings (Central and South America, sub-Saharan Africa and Asia). Modes of transmission include the following:

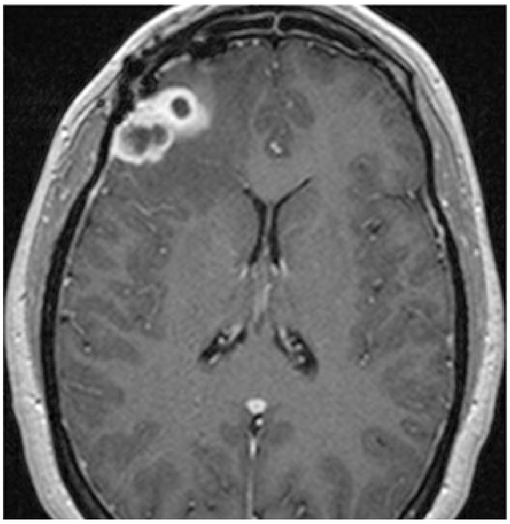


FIGURE 2.9-18. **Brain abscess.** Postcontrast MRI of the brain shows ring-enhancing lesions in the lateral right frontal lobe, with "daughter" lesions (smaller adjacent rings of enhancement) also noted. (Reproduced with permission from USMLE-Rx.com.)

- **Direct spread (25–50% of cases):** Caused by paranasal sinusitis (frequently affects young men and is often caused by *Streptococcus milleri* [of the α-hemolytic viridans streptococcus]), otitis media, mastoiditis, or dental infection
- **Direct inoculation:** History of head trauma or neurosurgical procedures
- **Hematogenous spread (25% of cases):** Often shows an MCA distribution with multiple abscesses that are poorly encapsulated and located at the gray-white junction

History/PE

Headache (most common), drowsiness, inattention, confusion, and seizures are early symptoms, followed by signs of increasing ICP and focal neurologic deficits.

KEY FACT

The classic clinical triad of headache, fever, and a focal neurologic deficit is present in 50% of cases of brain abscess.

Diagnosis

- CT scan will show a ring-enhancing lesion with a low-density core.
- **Most accurate test:** MRI has a higher sensitivity for early abscesses and posterior fossa lesions.
- CSF analysis is not necessary and may precipitate brainstem herniation.
- Lab values may show peripheral leukocytosis, ↑ ESR, and ↑ C-reactive protein (CRP).

Treatment

- **IV antibiotics:** Metronidazole + a third-generation cephalosporin ± vancomycin for 6 to 8 weeks. The physician should obtain serial CT/MRIs to follow resolution. Lesions <2 cm can often be treated medically.
- Surgical drainage (aspiration or excision) may be necessary for diagnostic and/or therapeutic purposes.
- Dexamethasone with taper may be used in severe cases to ↓ cerebral edema; IV mannitol

may be used to ↓ ICP. Prophylactic anticonvulsants should be given.

KEY FACT

In general, LP is contraindicated for a patient with a mass lesion in the brain because of the potential but life-threatening risk for uncal or cerebellar herniation.

DISORDERS OF THE NEUROMUSCULAR JUNCTION

MYASTHENIA GRAVIS

Myasthenia gravis (MG) is an autoimmune neuromuscular junction disorder caused by nicotinic acetylcholine receptor autoantibodies. These autoantibodies bind to nicotinic acetylcholine receptors on the postsynaptic neuromuscular membrane, which results in a fatiguing muscular weakness syndrome with a sex-specific age distribution (women aged 20–30 years; men aged 60–80 years). Seventy-five percent of patients have thymic disease (85% thymic hyperplasia; 15% thymoma; Fig. 2.9-19).

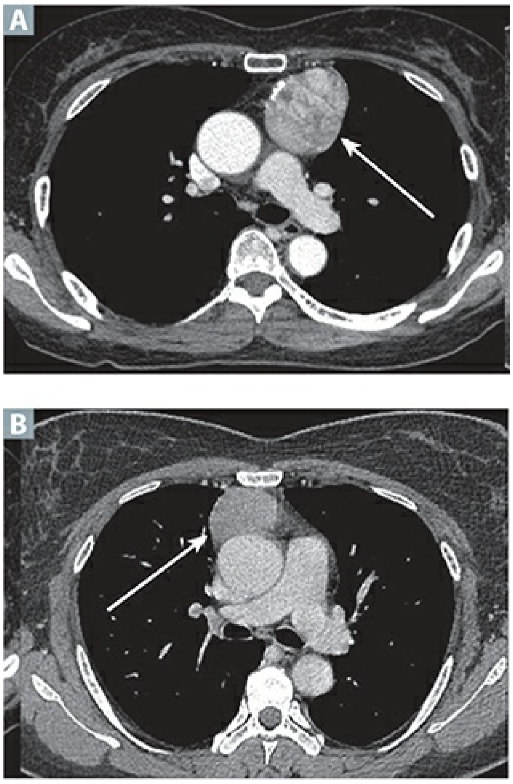


FIGURE 2.9-19. **CT image of an encapsulated thymoma *(arrow)* in a 61-year-old female with myasthenia gravis set to undergo surgical resection.** (Reproduced with permission from Lee JH, Park CM, Park SJ, et al. Value of computerized 3D shape analysis in differentiating encapsulated from invasive thymomas. *PLoS One.* 2015;10[5]:e0126175. Published 2015 May 4. doi:10.1371/journal.pone.0126175.)

History/PE

- **Hallmark: Muscle fatigability.** Small, often-used muscles (eyelid, jaw muscles) are more sensitive to AChR-Ab interference, which results in ocular symptoms (most common initially: ptosis, diplopia), facial weakness, bulbar symptoms (chewing fatigue, dysphagia, dysarthria), and upper/lower extremity muscle weakness notably worse at the end of the day and with sustained activity.

- **Other distinguishing features:** Absence of autonomic symptoms (only a neuromuscular junction disorder) along with normal pupillary responses, sensations, and deep tendon reflexes. Progressive muscle weakness occurs with increased use. See Table 2.9-16.

TABLE 2.9-16. Myasthenia Gravis vs Lambert-Eaton Myasthenic Syndrome

KEY FEATURES	MYASTHENIA GRAVIS	LAMBERT-EATON MYASTHENIC SYNDROME
Cause	Acetylcholine receptor (AChR) autoantibodies that bind to the postsynaptic nicotinic ACh-Rs on the neuromuscular junction (NMJ)	VGCC autoantibodies that bind to presynaptic VGCCs on the NMJ + autonomic nervous system
Using muscles	Worsens symptoms (muscle fatigability)	Temporarily improves symptoms (muscle usability)
Testing deep tendon reflexes	Initially normal → Worsen with repeated testing	Initially diminished/absent → Improve with repeated testing
Eye symptoms	Common	Less common
Autonomic dysfunction	Absent	Present

- **Myasthenic crisis:** Rapid worsening of muscular weakness that is life threatening because it can lead to respiratory distress and airway obstruction due to respiratory and bulbar muscle fatigue, respectively. Precipitating factors include infection (most common), surgery, and drugs. Notably, antibiotics (aminoglycosides, fluoroquinolones), hydroxychloroquine, and β-blockers can precipitate crisis and/or worsen symptoms. Avoid if possible.

Diagnosis

- **Best initial test:** Acetylcholine receptor autoantibodies (AChR-Ab). If seronegative for AChR-Ab and symptoms suggest MG, the case calls for muscle-specific kinase (MuSK) autoantibodies.
- **Most accurate test:** Electromyography (EMG). It shows muscle fatigability with a decremental response to repetitive nerve stimulation. This occurs as endogenous acetylcholine (ACh) stores are depleted and AChR-Ab outcompete endogenous ACh for nicotinic receptors.
- **Best initial imaging test:** Contrast CT or MRI of the chest to evaluate the anterior mediastinum for thymic disease.
- **Bedside tests:** Application of ice for 1 to 2 minutes on the eyelid to relieve ptosis by decreasing acetylcholinesterase activity and increasing endogenous ACh in the synapse. Edrophonium is a short-acting acetylcholinesterase antagonist that raises endogenous ACh in the synapse to briefly improve motor symptoms.

MNEMONIC

Because patients with myasthenic gravis characteristically lack autonomic symptoms, the presence of autonomic symptoms suggests treatment (anticholinesterase) toxicity—

DUMBELLS signs/symptoms:

Diarrhea
Urination
Miosis
Bradycardia + **B**ronchorrhea + **B**ronchospasms
Emesis
Lacrimation
Lethargy
Salivation

KEY FACT

Myasthenia gravis presents with eye/bulbar muscle symptoms that worsen with use, initially normal reflexes that worsen with testing, with *no* autonomic dysfunction—classically in a patient with an anterior mediastinal mass (thymic hyperplasia/thymoma).

Treatment

- **Acute exacerbations/myasthenia crisis:** Plasmapheresis/exchange or intravenous immunoglobulin (IVIG) ± steroids. Monitoring vital capacity, maximum inspiratory pressure, and airway patency can call attention to invasive or noninvasive ventilation needs.
- **Chronic drug therapies:** Acetylcholinesterase inhibitors (best initial treatment; pyridostigmine) ± glycopyrrolate (antimuscarinic drug used to control autonomic side effects of anticholinesterase treatment). Most need immunotherapy initially with steroids, followed by a transition to nonsteroidal immunosuppressants such as azathioprine.
- **Anticholinesterase drug toxicity:** Because patients with MG lack autonomic symptoms, alertness is required for patients presenting with widespread cholinergic activation.
- **Surgery:** Thymectomy indicated for all patients with thymomas *and* for all patients <60 years of age with mild to moderate disease.

LAMBERT-EATON MYASTHENIC SYNDROME

Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune neuromuscular junction disorder caused by voltage-gated calcium channel (VGCC) autoantibodies. These autoantibodies bind to VGCCs on the presynaptic neuromuscular membrane and other presynaptic terminals located throughout the autonomic nervous system → ↓ ACh release. This results in a muscular weakness syndrome with autonomic dysfunction. It can occur as a non-paraneoplastic syndrome or a paraneoplastic syndrome (more common) that is classically associated with small cell lung carcinoma (62% of cases).

KEY FACT

Repetitive nerve stimulation reveals a characteristic incremental response in Lambert-Eaton myasthenic syndrome (muscle usability) but shows a decremental response in myasthenia gravis (muscle fatigability).

History/PE

- **Hallmark:** Muscle usability. LEMS is characterized by slow-onset proximal muscle weakness (difficulty rising from chair, walking, combing hair, reaching upward on shelves) that is distinguished from myositis as creatine kinase (CK) levels are normal and myalgia is absent. The symptoms of LEMS improve with activity (muscle usability) as repeated depolarizations of presynaptic terminals help overcome the autoantibody blockade of presynaptic VGCCs.
- **Other distinguishing features:** Presence of autonomic dysfunction. Autoantibodies to presynaptic VGCCs impair Ach release in the neuromuscular junction and throughout the autonomic nervous system. This results in autonomic dysfunction, including xerostomia, erectile dysfunction, constipation, and impaired pupillary light response. Initial deep tendon reflexes are diminished/absent but increase with repeated testing due to “muscle usability.”

Diagnosis

- **Best initial test:** Anti-P/Q–type VGCC autoantibodies.
- **Most accurate test:** EMG. Shows muscle usability with an incremental response to repetitive nerve stimulation as repeated depolarizations of presynaptic terminals helps overcome the autoantibody blockade of presynaptic VGCCs.
- **Best initial imaging test:** CT or MRI facilitates evaluation for underlying malignancy, classically small cell lung cancer (contrast CT chest).

Treatment

- Paraneoplastic LEMS → treatment of underlying malignancies (classically small cell lung carcinoma).
- Amifampridine (3,4-diaminopyridine [3,4-DAP]) or guanidine. Both ↓ potassium efflux from presynaptic neurons → prolonged depolarization → ↑ ACh release. Acetylcholinesterase inhibitors (pyridostigmine) are also used to ↑ ACh.
- IVIG followed by oral immunosuppressive agents if persistent disease despite medical therapy and treatment of underlying malignancy.

KEY FACT

Lambert-Eaton myasthenic syndrome presents with proximal muscle weakness that briefly improves with use, initially diminished/absent reflexes that improve with testing, and autonomic dysfunction—classically in a patient with a lung mass on imaging.

BOTULISM

Symmetric descending paralysis caused by ingestion of *Clostridium botulinum* spores or exposure to spores in soil of endemic regions (California, Utah). Disease calls for IV botulism IG and respiratory support. Consider in any infant with bulbar palsies, ptosis, constipation, or hypotonia. Avoid honey to prevent exposure in young infants (see Table 2.9-17).

TABLE 2.9-17. **Types of Botulism**

	FOODBORNE	INFANT	WOUND
Etiology	Ingestion of pre-formed toxin	Ingestion of spores	Spores in contaminated wounds (eg, IV drug use)
Incubation	12–36 hours	Days to 4 weeks	4–14 days
Treatment	Equine botulinum antitoxin	Human botulism immunoglobulin	Equine botulinum antitoxin Surgical debridement
Prevention	Sterilize food (autoclaving) Boil food twice before canning	Avoid giving honey to infants <12 months	Avoid using IV drugs Follow medically sound wound care

DEMYELINATING DISORDERS

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a demyelinating disorder of the CNS of unclear etiology, but it is thought to be immune mediated. The female-to-male ratio is 2:1, and it is typically diagnosed between 20 and 40 years of age. MS becomes more common with increasing distance from the equator during childhood and in patients with a history of autoimmune disease. MS has been associated with the HLA-DRB1 locus. Subtypes are relapsing remitting (most common), primary progressive, secondary progressive, and progressive relapsing.

History/PE

- Multiple neurologic complaints that are separate in time and space and are not explained by a single lesion. As the disease progresses, permanent deficits accumulate.
- Bilateral internuclear ophthalmoplegia caused by bilateral medial longitudinal fasciculus (MLF) lesions is classic for MS.
- Limb weakness, gait unsteadiness, paresthesias, Lhermitte sign (electric shock sensation that radiates down the spine or limbs), blurry vision, vertigo, nystagmus, urinary retention, sexual and bowel dysfunction, depression, and cognitive impairment are also seen. Symptoms classically worsen transiently with hot showers.
- Attacks are unpredictable but on average occur every 1.5 years, lasting for 2 to 8 weeks.
- Neurologic symptoms can come and go or be progressive. Those with a relapsing and remitting history have the best prognosis.

KEY FACT

Pregnancy may be associated with a ↓ in MS symptoms, but this comes with increased risk of exacerbation postpartum.

Diagnosis

- Thorough history and physical examination are important.
- **Most accurate tests:** Use MRI and LP for definitive diagnosis.
- MRI (diagnostic test of choice for MS) shows multiple asymmetric, often periventricular, white matter lesions (Dawson fingers), especially in the corpus callosum. Active lesions are enhanced with gadolinium.
- CSF reveals ↑ IgG index or at least two oligoclonal bands not found in the serum (nonspecific).
- LP is only indicated for atypical cases where the diagnosis is unclear clinically and by MRI.

Treatment

- **Acute exacerbations:** High-dose IV corticosteroids. Plasma exchange in patients who do not respond to corticosteroids
- **Disease-modifying medications:** Natalizumab and ocrelizumab are highly effective in patients who haven't responded to other therapies. Risk of PML with natalizumab. Patients with less active disease can be started on oral medications, such as dimethyl fumarate or fingolimod. Beta-interferon therapy and glatiramer have the highest safety profiles but decreased effectiveness.
- Symptomatic therapy includes baclofen for spasticity, cholinergics for urinary retention, anticholinergics for urinary incontinence, carbamazepine or amitriptyline for painful paresthesias, and antidepressants for clinical depression.

GUILLAIN-BARRÉ SYNDROME

An acute, rapidly progressive demyelinating autoimmune disorder of the peripheral and cranial nerves that results in weakness. Associated with recent *Campylobacter jejuni* infection, viral infection, or influenza vaccine (in extremely rare cases). This preceding infection triggers an autoimmune response against the myelin or axon of peripheral nerves. Approximately 85% of patients make a complete or near-complete recovery (may take up to 1 year). The most common type is called acute inflammatory demyelinating polyneuropathy. Another subtype is Miller Fisher syndrome, characterized by ophthalmoplegia, ataxia, and absent reflexes.

MNEMONIC

The 4 As of Guillain-Barré syndrome—

*A*cute inflammatory demyelinating polyradiculopathy
*A*scending paralysis
*A*utonomic neuropathy
*A*lbuminocytologic dissociation (increased albumin in CSF)

History/PE

- Classically presents with progressive (hours to days), symmetric, ascending paralysis (distal to proximal) and areflexia. Paralysis can progress to involve the trunk, diaphragm, and cranial nerves. Twenty-five percent of patients experience respiratory failure and may require intubation.
- Autonomic and sensory nerves may also be affected, leading to glove-and-stocking distribution paresthesias and autonomic dysregulation (eg, orthostatic hypotension, bladder dysfunction, arrhythmias).
- Increased risk of hyponatremia (poor prognostic factor).

Diagnosis

- Evidence of diffuse demyelination is seen on nerve conduction studies, which show ↓ nerve conduction velocity.
- Diagnosis is supported by an elevated CSF protein level >55 mg/dL and normal WBC count (albuminocytologic dissociation).

KEY FACT

Remember that ascending paralysis with normal CSF findings and without autonomic dysfunction is characteristic of tick-borne paralysis, not Guillain-Barré syndrome.

Treatment

- Frequent monitoring of maximal negative inspiratory force (NIF) and vital capacity can determine whether the patient should be admitted to the intensive care unit (ICU) for impending respiratory failure.
- Plasmapheresis and IVIG are first-line. Corticosteroids are not indicated.
- Aggressive physical rehabilitation is imperative.

NEURODEGENERATIVE DISORDERS

Neurodegenerative disorders commonly present with cognitive complaints. Early on, it can be difficult to determine whether this is due to normal aging or mild or major neurocognitive impairment (see Table 2.9-18).

TABLE 2.9-18. **Clinical Approach to Neurocognitive Disorders**

CONDITION	CRITERIA
Normal aging	Age >60 years, normal MMSE (>27/30) Executive function issues in attention span, problem solving, acquiring new information Word-finding difficulties (expressive aphasia) Advanced sleep-wake cycle (eg, go to sleep 7 PM, wake at 3 AM) Generally, no loss of functional ability of daily living occurs (ADLs, IADLs)
Mild neurocognitive disorder	Deficit in at least one neurocognitive domain (executive function, perceptual-motor function, language, learning + memory, social cognition, complex attention) that cannot be related to normal aging Abnormal MMSE (23–27/30) Generally, some functional ability is lost, but patient can still function in daily living (ADLs) with certain constraints (IADLs)
Major neurocognitive disorder = dementia	Significant decline in one or more neurocognitive domains Abnormal MMSE (usually <24/30) Functional ability is lost + assistance with ADLs/IADLs is needed Most important risk factor is age Classic **4 As** of dementia: 1. **A**mnesia (forgetting) 2. **A**phasia (forgetting words, struggling to communicate, comprehension issues [nods to pretend]) 3. **A**praxia (cannot perform preprogrammed motor tasks) → cannot do job/ADLs/IADLs → eating, dressing, using a TV remote, driving a car, mobility (walking) issues 4. **A**gnosia (struggling to interpret senses): Visual (cannot recognize people), auditory (cannot recognize a voice as familiar), alexia (inability to read or comprehend written language), sensing full bladder → incontinence, pain→ general irritability Contrast delirium (acute, level-of-consciousness changes, cognition waxes/wanes, usually reversible, EEG abnormal with "acutely sick brain") versus dementia (exhibits no changes in level of consciousness, usually irreversible, chronic + gradually progressive cognitive decline, EEG normal) Ruling out reversible causes via history (especially medications, social history for depression [loss of spouse] → pseudodementia), physical examination, and laboratory (CBC + differential, thyroid function tests, vitamin levels (B$_9$/B$_{12}$), chemistry panel, infection diseases (VDRL [syphilis] + HIV screening) ± imaging (CT/MRI)
REVERSIBLE CAUSES OF DEMENTIA	IRREVERSIBLE CAUSES OF DEMENTIA
Hypothyroidism Neurosyphilis/HIV dementia (depending on stage/treatment) Vitamin B$_{12}$, B$_9$ deficiencies Thiamine deficiency (alcohol overuse → Wernicke aphasia) Medications (eg, benzodiazepines, anticholinergics) Normal-pressure hydrocephalus Pseudodementia Chronic subdural hematoma (fall → bridging veins tear)	Alzheimer disease (overall 66% of cases) Vascular (multi-infarct dementia; overall 5%–10% cases) Parkinson disease dementia, Lewy body dementia (20%) Huntington disease, frontotemporal dementia Unresectable brain neoplasm, Wilson disease, PML Prion diseases (Creutzfeldt-Jakob disease) Neurosyphilis/HIV dementia (depending on stage/treatment) Thiamine deficiency (alcohol abuse → Korsakoff)

ADLs, Activities of daily living; *IADLs*, instrumental activities of daily living; *MMSE*, Mini Mental State Examination (score range depends on education level).

DEMENTIA

Dementias are progressive, chronic diseases characterized by the *continuous degeneration of neurons*. So focus on the onset of early presenting features to diagnose them in vignettes, as middle-to-late findings can overlap. Table 2.9-19 and the sections that follow contrast the time course, diagnostic criteria, and treatment of common types of dementia.

TABLE 2.9-19. **Types of Dementia**

TYPE	TIME COURSE, KEY EARLY PRESENTATION	PATHOLOGIC FINDINGS	IMAGING/STUDIES
Alzheimer disease	Gradual, early memory impairment	Extracellular neuritic plaques (Image A, *red arrows:* amyloid β trapping neuritic processes) + intracellular neurofibrillary tangles (Image B, *black arrow:* hyperphosphorylated tau proteins) + intracellular Hirano bodies (rod-shaped aggregates actin/associated proteins, especially in hippocampus)	MRI/CT → diffuse cortical atrophy (especially in temporal/parietal lobes) + hippocampal atrophy → hydrocephalus ex vacuo = ventriculomegaly, which is in proportion to increased sulcal size
Vascular dementia	Stepwise, abrupt decline after each overt/subclinical stroke	Strokes in multiple areas of cerebral cortex and subcortical regions	Brain imaging revealing evidence of old infarctions (including lacunes) or extensive deep white-matter changes secondary to chronic ischemia
Frontotemporal dementia (Pick disease)	Gradual, early personality ± language changes	Neuronal intracellular accumulations of ubiquitinated TDP-43 proteins ± Pick bodies	MRI revealing unilateral or bilateral frontal and/or temporal lobe atrophy → hydrocephalus ex vacuo Fluorodeoxyglucose-positron emission tomography (FDG-PET) → frontotemporal hypoperfusion + hypometabolism
Normal-pressure hydrocephalus	Gradual, early gait ataxia	↓ CSF absorption → ↑ CSF → lateral ventricles expand → stretch corona radiata → **W**obbly, **W**et, **W**acky	MRI > CT → ventriculomegaly without cortical atrophy = without sulcal enlargement
Creutzfeldt-Jakob disease	Abrupt, rapidly progressive dementia + startle myoclonus	Real-time quaking-induced conversion (RT-QuIC) detection of prions, spongiform degeneration	MRI (diffusion-weighted imaging) → ↑ T2 + FLAIR intensity in the putamen + caudate EEG → periodic sharp, triphasic synchronous discharge complexes
Dementia with Lewy bodies	Gradual, more rapid than Alzheimer disease; hallucinations, daily fluctuations in cognition; parkinsonism; REM sleep behavior disorder	Round, eosinophilic inclusions of α-synuclein in cerebral cortex (Image C) (dementia with Lewy bodies [DLB]) or subcortical (basal ganglia)/midbrain regions (Parkinson disease dementia)	MRI → cortical atrophy with limited hippocampal atrophy (vs Alzheimer disease)

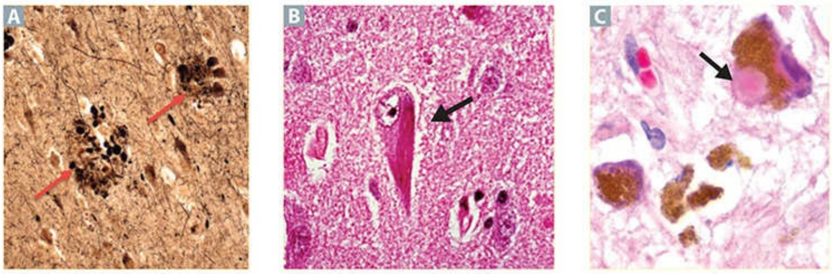


Image A reproduced with permission from USMLE-Rx.com. Image B reproduced with permission from Dr. Kristine Krafts. Image C Modified with permission from Werner CJ, Heyny-von Haussen R, Mall G, Wolf S. Proteome analysis of human substantia nigra in Parkinson's disease. *Proteome Sci*, 2008;6:8. doi:10.1186/1477-5956-6-8.

KEY FACT

In HIV-associated neurocognitive disorder (HAND) can occur in HIV/AIDS patients regardless of HIV treatment status. HAND is partly caused by HIV-infected microglia in the

CNS. Dx: Diagnosis of exclusion; early findings include mild cognitive impairment that can progress to HIV-associated dementia. Tx: antiretroviral therapy; avoid efavirenz due to CNS side effects.

ALZHEIMER DISEASE

Alzheimer disease (AD) is a chronic, progressive neurodegenerative disease that represents the most common cause of dementia (66%). Degeneration of cholinergic circuits → diffuse atrophy of cortex + subcortex (hippocampus = hallmark of recent memory impairment). Age is the most important risk factor for sporadic AD, as 95% of patients present at age >65. The apolipoprotein E gene can be harmful or protective (ε4 allele → amyloid precursor protein [APP] → promotes formation of amyloid β [pathologic]). ε2 allele → APP → promotes formation of amyloid α (nonpathologic). ↑ number = ↑ risk. Early-onset AD (5% cases, <65 years of age) is familial (APP + presenilin 1,2 gene mutations) and associated with Down syndrome (APP on chromosome 21).

History/PE

- **Neurocognitive dysfunction:** Degeneration of cholinergic circuits to hippocampus → declarative episodic recent memory impairment = earliest, most important clinical finding. Continued degeneration of cortex + subcortex → progressive memory impairments (eg, long-term memories) later in the disease. Other early-to-intermediate findings include executive dysfunction with judgment/problem solving (poor work performance) + visuospatial impairments (getting lost in familiar places) + language deficits (naming, comprehension, fluency). Other cognitive domains = intermediate-to-late findings.
- **Behavioral** + **psychiatric:** Middle to late in the course of AD. Patients exhibit personality changes and can become apathetic, socially disengaged, irritable, aggressive, and psychotic.
- **Incontinence** + **motor:** Bowel/bladder incontinence + motor dysfunction (eg, apraxia for learned motor tasks) are *not* present in the early-to-intermediate course of AD (mainly late findings).

MNEMONIC

Symptom onset distinguishes AD from normal-pressure hydrocephalus (NPH):

Alzheimer (DUM): Dementia (early, short-term memory) > **U**rinary incontinence > **M**otor
NPH (MUD): Motor (early, gait ataxia) > **U**rinary incontinence > **D**ementia

Diagnosis

Clinical diagnosis:

- **Imaging:** MRI/CT reveals diffuse cortical (especially temporal/parietal lobes) + hippocampal atrophy → hydrocephalus ex vacuo
- **Pathologic examination** reveals extracellular neuritic plaques (amyloid β entrapping neuritic processes → cerebral amyloid angiopathy → lobar hemorrhage) + intracellular neurofibrillary tangles (hyperphosphorylated tau proteins) + intracellular Hirano bodies (rod-shaped aggregates actin/associated proteins, especially in hippocampus)

Treatment

- **Best first-line treatment of mild to moderate AD:** Acetylcholinesterase inhibitors. Degeneration of cholinergic neurons → widespread cholinergic deficiency → treatment with acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) → modest improvement in cognitive + global functioning. No evidence for altering disease progression. Adverse effects include nausea, dizziness, and insomnia, among other cholinergic side effects.
- *Avoid* anticholinergic medications!
- Vitamin E can be supplemented for its antioxidant role in mild to moderate dementia. Although evidence is inconclusive, it is often prescribed due to its good safety profile.
- Moderate to severe AD → add memantine → N-methyl-D-aspartate (NMDA) receptor antagonist → ↓ glutamate excitotoxicity → neuroprotective → modifies progressive symptomatic decline. Adverse effects include dizziness, confusion, and hallucinations.

VASCULAR DEMENTIA

Dementia associated with a history of stroke and cerebrovascular disease. Vascular dementia is the second most common type of dementia.

History/PE

- Stepwise decline in cognitive ability, with impaired executive function often preceding memory deficits
- May be associated with other symptoms of stroke, such as sensory or motor deficits
- Risk factors include age, hypertension, diabetes, coronary artery disease, embolic sources, and a history of stroke

KEY FACT

If a patient shows abrupt changes in symptoms (especially motor symptoms) over time rather than a steady decline, think vascular dementia.

Diagnosis

The diagnosis is made when there is dementia or mild cognitive impairment and all of the following:

- Cerebrovascular disease as evidenced by history/PE or neuroimaging
- Clinical course that is abrupt, stepwise, or related to stroke
- Symptoms not better explained by other disorders such as progressive nonvascular dementia

Treatment

Protocols for the prevention and treatment of vascular dementia are the same as those for stroke, including treatment of risk factors for atherosclerotic cardiovascular disease (ASCVD).

FRONTOTEMPORAL DEMENTIA (PICK DISEASE)

A rare progressive, irreversible neurodegeneration of mainly the frontal and/or temporal lobes. Frontotemporal dementia (FTD) manifests as early-onset dementia (50s to 60s) and encompasses a spectrum of subtypes that present with predominately frontal lobe (Pick personality/behavioral changes/possibly motor) and/or temporal lobe (aphasia) features.

History/PE

- **Behavioral variant FTD** (most common) is characterized by early progressive changes in behavior that represent a dramatic, persistent shift in predisease personality. Representing degeneration of the frontal cortex, presentations include disinhibition, socially inappropriate behavior, apathy, loss of empathy/sympathy, hyperorality (binge eating, putting objects in mouth), compulsive behaviors, and depending on subtype/locations of degeneration, motor symptoms.
- **Primary progressive aphasia** represents an aphasia subtype of FTD that presents with an insidious onset and gradual progression of speech/language impairment such as speech apraxia ± word finding/usage/comprehension difficulties. Early in the disease, other cognitive domains remain intact.

Diagnosis

- Clinical diagnosis
- **Imaging:**
  - MRI reveals unilateral or bilateral frontal and/or temporal lobe atrophy → hydrocephalus ex vacuo
  - FDG-PET reveals frontotemporal hypoperfusion + hypometabolism
- **Pathologic examination** reveals neuronal intracellular accumulations of ubiquitinated TDP-43 proteins ± Pick bodies (spherical [round] aggregates of hyperphosphorylated tau proteins)

Treatment

No disease-modifying therapies exist. Supportive care only (eg, for depression, agitation, insomnia).

NORMAL-PRESSURE HYDROCEPHALUS

A relatively rare, potentially reversible form of dementia that arises in adults age >60. Normal-pressure hydrocephalus (NPH) is a form of chronic communicating hydrocephalus: ↓ CSF absorption → ↑ CSF → enlargement of ventricles → lateral ventricles expand → stretching of the corona radiata → gait ataxia (early, altered corticospinal tract) + urinary urgency/frequency/incontinence (loss detrusor inhibition) + dementia. NPH can be idiopathic or arise secondarily from damage to the arachnoid granulations (impairs CSF absorption) triggered by inflammatory (meningitis) and hemorrhage-induced (intraventricular/subarachnoid) causes.

Q

A 71-year-old woman is brought to her primary care physician's office by her son, who is concerned that she has had worsening recent memory, difficulty participating in her daily activities, restlessness, and difficulty sleeping for the past year. She scores a 22 on the Mini-Mental State Exam (MMSE). What is the most likely diagnosis?

History/PE

Pressures: NPH is characterized by a normal opening pressure on LP. Continuous ICP monitoring in studies shows normal or episodically ↑ ICP. As such, NPH is a form of hydrocephalus that occurs in the absence of diffusely ↑ ICP symptoms (papilledema, headaches, nausea/vomiting, vision loss). The ↑ CSF in NPH causes regional, not diffuse, ↑ ICP via the stretching of the lateral ventricles → stretching of the corona radiata → classic triad of gait ataxia (wobbly), urinary incontinence (wet), and dementia (wacky).

- **Gait ataxia (wobbly)** is an early hallmark sign. The magnetic gait is like the shuffling gait seen with Parkinson disease (PD) (slow, wide based). It is distinguished by arm swing preservation + lack of other motor findings (tremor).
- **Urinary incontinence (wet).** Early in disease, urinary urgency/frequency is more common. Later in disease, urinary incontinence is more common and is accompanied by apathy.
- **Dementia (wacky)** evolves over months to years after gait dysfunction with psychomotor delay, decreased concentration/attention, executive dysfunction, and apathy.

Diagnosis

- **Clinical:** Patients do *not* need to have the complete triad of gait ataxia, urinary incontinence, and dementia.
- **Gait dysfunction** is key, as it can be the only symptom and must be present for the diagnosis. The physician should establish the presence of urinary urgency/frequency/incontinence via history and dementia via cognitive testing.
- **Best initial imaging test:** MRI > CT and shows ventriculomegaly without cortical atrophy = without sulcal enlargement (see Fig. 2.9-20).

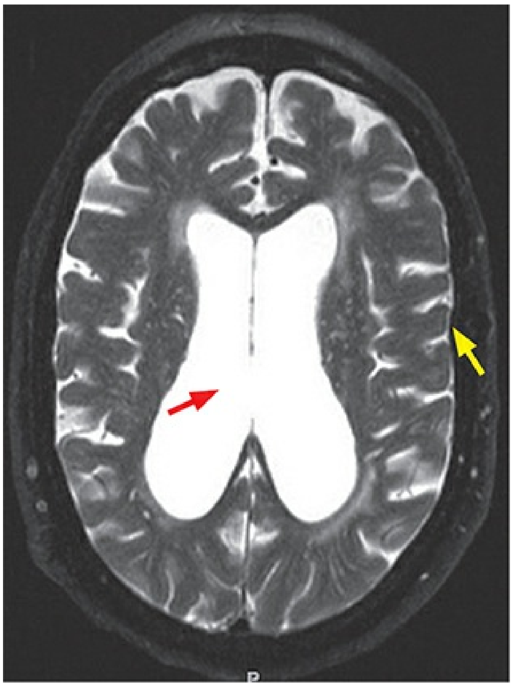


FIGURE 2.9-20. **Normal-pressure hydrocephalus.** T2-weighted MRI from a 60-year-old woman with early gait ataxia, slowly developing urinary incontinence, and dementia shows marked dilation of the lateral ventricles (*red arrow*). This is out of proportion to the sulcal enlargement (ie, without sulcal enlargement) (*yellow arrow*). (Reproduced with permission from USMLE-Rx.com.)

- **Best confirmatory test**: Improvement of symptoms following LP (opening pressure is normal/slightly ↑).

KEY FACT

Classic triad of NPH in order of onset = “**W**obbly (gait ataxia), **W**et (urgency/incontinence), and **W**acky (dementia).”

Treatment

Definitive treatment: Ventriculoperitoneal (VP) shunting. A lumbar drainage trial, over the course of 2 to 7 days, can be used to determine potential response to VP shunting. Predominant gait symptoms indicate a favorable surgical response, while the presence of moderate to severe dementia does not.

CREUTZFELDT-JAKOB DISEASE

Although it is the most common prion disease, Creutzfeldt-Jakob disease (CJD) remains an extremely rare form of dementia. CJD occurs when an abnormal protease-resistant prion protein accumulates in the brain, causing spongy degeneration, neuronal loss, and astrocytic proliferation.

History/PE

- CJD causes a subacute dementia with ataxia and/or startle-induced myoclonic jerks, with rapid clinical progression that is noted weeks to months after symptom onset.
- New-variant CJD (mad cow disease) is a more slowly progressive prion disease seen in younger people with a history of eating contaminated beef or contaminated human brains (kuru).
- Iatrogenic CJD can be seen after ophthalmologic or neurosurgical procedures such as corneal transplant due to poor equipment sterilization.

KEY FACT

CJD’s rapid progression and presence of myoclonus distinguish it from other dementias.

A

Alzheimer disease is the likely diagnosis. The key differences between Alzheimer disease and normal aging are that in normal aging, patients can perform their activities of daily living, complain of memory loss yet provide detailed information about their forgetfulness, and have a score >27 on the MMSE.

Diagnosis

- Definitive diagnosis can be made only by brain biopsy or autopsy, but clinical features, imaging, and lab results are sufficient to make a probable diagnosis.
- ↑ 14-3-3 protein in CSF and periodic sharp wave complexes on EEG.
- Real-time quaking-induced conversion (RT-QuIC) is a new method to detect real-time

protein misfolding within CSF samples.

- Brain MRI may show hyperintensity in the caudate and putamen (“hockey stick sign”) or a cortical ribboning pattern.
- Differential diagnosis includes paraneoplastic syndromes, drug induced, and autoimmune encephalitis. Probable diagnosis of CJD is made when there is a rapid progression of symptoms with no other cause identified by MRI, EEG, or CSF samples, plus corroborating findings as listed in this section.

Treatment

Symptomatic management. Most patients die within 1 year of symptom onset as there is no cure and progression cannot be halted.

LEWY BODY DEMENTIA

Lewy body dementia is an umbrella term for PD (Lewy body) dementia and dementia with Lewy bodies (DLB)—distinguished by the 1-year rule (see Diagnosis). DLB is the second most common cause of dementia (10%–20% of cases) and classically presents in patients age >65 and classically presents in patients age >65 with associated depression and suicidality.

History/PE

Classic triad of dementia + parkinsonism + visual “hallewynations.”

- Dementia is characterized by executive and visuospatial dysfunction.
- Parkinsonism = extrapyramidal motor symptoms = **TRAP** (**T**remor, **R**igidity, **A**kinesia/bradykinesia, **P**ostural instability).
- Visual hallucinations are well-formed + detailed (animals, people, abstract shapes/colors).
- Fluctuations are present in cognition, arousal, and attention (range from baseline to brief decline to strokelike).
- Rapid eye movement (REM) sleep behavior disorder → recurrent dream-related vocalizations/motor behaviors.

Diagnosis

Clinical diagnosis. One-year rule distinguishes PD dementia from DLB:

- DLB is diagnosed when cognitive impairment occurs with parkinsonism *or* within <1 year before parkinsonism.
- Parkinson disease dementia (PDD) is diagnosed when cognitive impairment occurs >1 year after parkinsonism.
- **Imaging:** MRI can show cortical atrophy with limited hippocampal atrophy (vs AD).
- **Pathology:** PD, PDD, and Lewy body dementia all have round, eosinophilic inclusions of α-synuclein (Lewy bodies) on pathologic examination and represent a disease spectrum. Inclusions are found in cortical cells (Lewy body dementia) and basal ganglia (PD, PDD).

Treatment

- **Acetylcholinesterase inhibitors for dementia:** Donepezil, galantamine, rivastigmine. Only used in AD + Lewy body dementias
- **Parkinsonian symptoms:** Similar to PD treatment with an emphasis on lower doses/slower titration to avoid exacerbating psychotic symptoms and hallucinations via ↑

dopamine

MOVEMENT DISORDERS

HUNTINGTON DISEASE

An autosomal dominant neurodegenerative disorder caused by excessive trinucleotide (CAG) repeats on chromosome 4 during spermatogenesis → abnormally long huntingtin protein → glutamate excitotoxicity via the NMDA-R→ degeneration of cerebrum + striatum (caudate + putamen) → loss of gamma-aminobutyric acid (GABA)/ACh, unbalanced dopamine (DA) activity → triad of motor (chorea), memory (executive dysfunction), and mood (irritability) symptoms. Huntington disease (HD) is slowly progressive, with only symptomatic treatments, and results in death in 10 to 20 years.

History/PE

Typically presents at 30 to 50 years of age with a family history that is indicative of anticipation (worsening/earlier symptoms in successive generations) and/or with relatives being misdiagnosed with psychiatric conditions/suicide. HD is characterized by a triad of motor, memory, and mood symptoms:

- **Motor:** Hyperkinetic early in disease (chorea, hyperreflexia, ↑ urine flow [incontinence], hyperhidrosis) early in disease → hypokinetic late in disease (rigidity, dystonia, bradykinesia, dysphagia, dysarthria). Chorea refers to random, brief, and irregular involuntary movements of the face, trunk, and limbs that flow between muscle groups. Early in the disease, chorea may manifest as restlessness/fidgetiness with delayed saccades.
- **Memory:** Cognitive impairment (executive dysfunction) + dementia.
- **Mood:** Symptoms of irritability, depression, and disruption of relationships precede chorea. Other psychiatric symptoms include obsessive-compulsive tendencies, aggression, anxiety, paranoia, delusions, hallucinations, suicidality, and psychosis, which may be mistaken for substance abuse.

Diagnosis

- Clinical features (motor, memory, mood) + family history (look for anticipation and misdiagnosed parents/grandparents with psychiatric conditions/suicide). Test creators may obscure these details in adopted children + genetic confirmation (CAG trinucleotide repeat expansions ≥36 repeats).
- **Imaging:**
  - FDG-PET early in disease shows altered glucose metabolism in striatum (caudate + putamen).
  - CT/MRI is important in diagnosing + assessing severity of disease (mainly). Late disease findings are marked atrophy of the cerebrum and the striatum (caudate + putamen). Atrophy, especially head of the caudate nuclei, → dilation of the lateral ventricles (hydrocephalus ex vacuo; see Fig. 2.9-21).

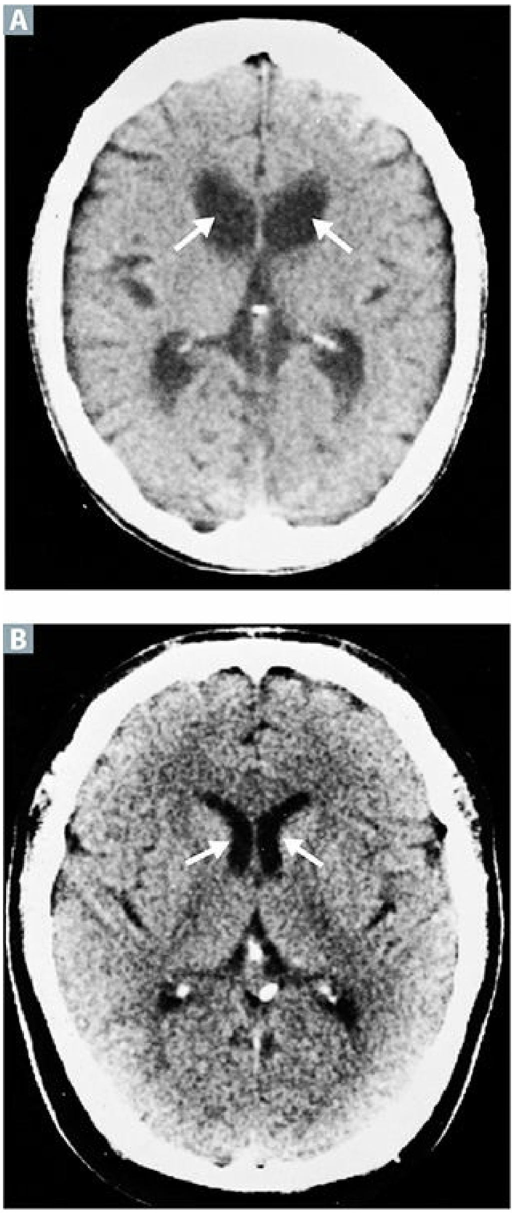


FIGURE 2.9-21. **Atrophy of the head of the caudate nuclei in Huntington Disease.** (**A**) Noncontrast CT in a 54-year-old patient with Huntington disease shows atrophy of the cerebrum and caudate nuclei (*arrows*) → dilation of the lateral ventricles (hydrocephalus ex vacuo). (**B**) A normal 54-year-old patient with normal cerebral mass, caudate nuclei (*arrows*), and lateral ventricles. (Modified with permission from Ropper AH, Samuels MA. *Adams & Victor's Principles of Neurology*, 9th ed. New York, NY: McGraw-Hill; 2009.)

Treatment

- No cure exists, and disease progression cannot be halted. Genetic counseling is recommended. Medical treatment is symptomatic and aimed at motor and associated psychiatric features. Mood disorders such as psychosis/agitation (atypical neuroleptics) and depression/anxiety (first-line treatment: selective serotonin reuptake inhibitors [SSRIs]) should be treated. When approaching treatment, it is important to consider the presence of chorea that interferes with functioning, as it guides drug selection.
- Chorea + psychiatric features result from unbalanced DA (loss of GABA/ACh) in brain:
- Chorea + comorbid depression, agitation ± psychosis → atypical neuroleptics (↓ risk of parkinsonism versus typical psychotics; monitor for adverse effects on motor function).

    - Chorea without comorbid depression, agitation, and/or psychosis → inhibit vesicular monoamine transporter 2 (VMAT2) (tetrabenazine or deutetrabenazine) = monoamine depleting agents → inhibit VMAT2 → ↓ DA packing into vesicles → ↓ DA release.

PARKINSON DISEASE AND PARKINSONISM

A progressive neurodegenerative disorder characterized by the loss of neuromelanin-containing dopaminergic neurons of the substantia nigra pars compacta (part of the basal ganglia). Pathologic examination reveals round, eosinophilic inclusions of alpha-synuclein in degenerating neurons. Typical age at presentation is >50 years, and risk factors include older age and family history of PD—with smoking being protective. PD is the most common hypokinetic movement disorder and is characterized by a unilateral hand tremor (“pill rolling”), oscillating rigidity (cogwheel), akinesia/bradykinesia (shuffling gait), and postural instability (frequent falls). PD is an idiopathic condition, but the motor symptoms (parkinsonism) can occur secondary to other neurodegenerative disorders, trauma, and medications. Treatment aims to ↑ dopaminergic activity (mainly) + ↓ cholinergic activity.

KEY FACT

The gaits of NPH and PD are similar. A significant difference between them, for diagnostic purposes, is the arm swing:

- PD gait = Reduced arm swing
- NPH gait = Preservation of arm swing

History/PE

Preclinical stage: Characterized by nonmotor signs of constipation, anosmia, sleep disturbances (REM disorders, restless leg syndrome, excessive sleepiness) and by mood disorders (depression, apathy, anxiety) that predate motor symptoms by up to 20 years.

Clinical: Characterized by motor signs (mainly), autonomic dysfunction, and neuropsychiatric features:

- **Motor signs:** Unilateral at onset with possible progression to the contralateral side. Asymmetric (worse on one side). See the **TRAPSS** mnemonic to recall the following motor signs = parkinsonism:
    - **Tremor:** Unilateral resting (4–6 Hz) tremor that improves with movement and worsens with distraction. “Pill-rolling” quality arises from 4- to 6-Hz frequency of thumb and finger movements.
    - **Rigidity:** Increased resistance to passive movement that can be uniform (lead pipe) but is classically cogwheeled, resulting in oscillating (“ratchet-like”) joint movements.
    - **Akinesia/bradykinesia:** Lack of or slowness of movements that can manifest as a narrow-based Shuffling gait with shortened strides + lack of arm swing; Small handwriting (micrographia); hypomimia (masked faces/limited facial expressions); hypophonia (soft speech).
    - **Postural instability:** Characterized by a flexed axial posture, loss of balance with stopping/turning, and an increased risk for frequent falls.
- **Autonomic dysfunction:** Neurogenic orthostatic hypotension (supine hypertensive and/or orthostatic hypotension), increased sweating, oily skin, constipation, sexual dysfunction,

urinary urgency, dysphagia.
- **Neuropsychiatric:** Dementia (advanced disease, see "Diagnosis"), executive/visuospatial dysfunction, visual hallucinations, delusions, sleep disorders (insomnia, restless leg syndrome, REM disorders, daytime sleepiness with sleep attacks, vivid dreams, sleep fragmentation [night awakenings]), depression, anxiety, apathy, anosmia.

MNEMONIC

Parkinson disease TRAPSS the body—

*T*remor ("pill rolling")
*R*igidity (cogwheeling)
*A*kinesia/bradykinesia
*P*ostural instability
*S*huffling gait
*S*mall handwriting (micrographia)

Diagnosis

Symptoms of parkinsonism (**TRAPSS**) may be present in other conditions (secondary). Clinical suspicion for alternative causes ↑ when there is lack of response to levodopa and and the following findings: a lack of adequate response to levodopa and the following findings:

Parkinsonism + ...

- Dysautonomia (mainly orthostasis) = multisystem atrophy-Parkinsonian Type (MSA-P) (Shy-Drager syndrome)
- Cerebellar ataxia = multisystem atrophy-cerebellar type (MSA-C)
- Oculomotor deficits (vertical gaze palsy) with no tremor = progressive supranuclear palsy (PSP)
- Impaired cognition, dystonia, sensory deficits, myoclonus = corticobasal degeneration
- Certain patient drugs (drug-induced ↓ dopamine activity):
  - Common causes: Typical > atypical antipsychotics, antiemetics (metoclopramide), vesicular dopamine depleters (tetrabenazine, reserpine), CCBs (flunarizine, cinnarizine).
  - Infrequent causes: Atypical antipsychotics (clozapine and quetiapine [it's "quiet" so use in PD psychosis]), mood stabilizer (lithium), antiepileptics (valproic acid, phenytoin), antiarrhythmic (amiodarone), MPTP (used in illegal drugs → destruction of substantia nigra → PD).
- Liver findings: Consider Wilson disease or hemochromatosis.
- Dementia = PDD *or* Lewy body dementia (see "Dementia" section).

KEY FACT

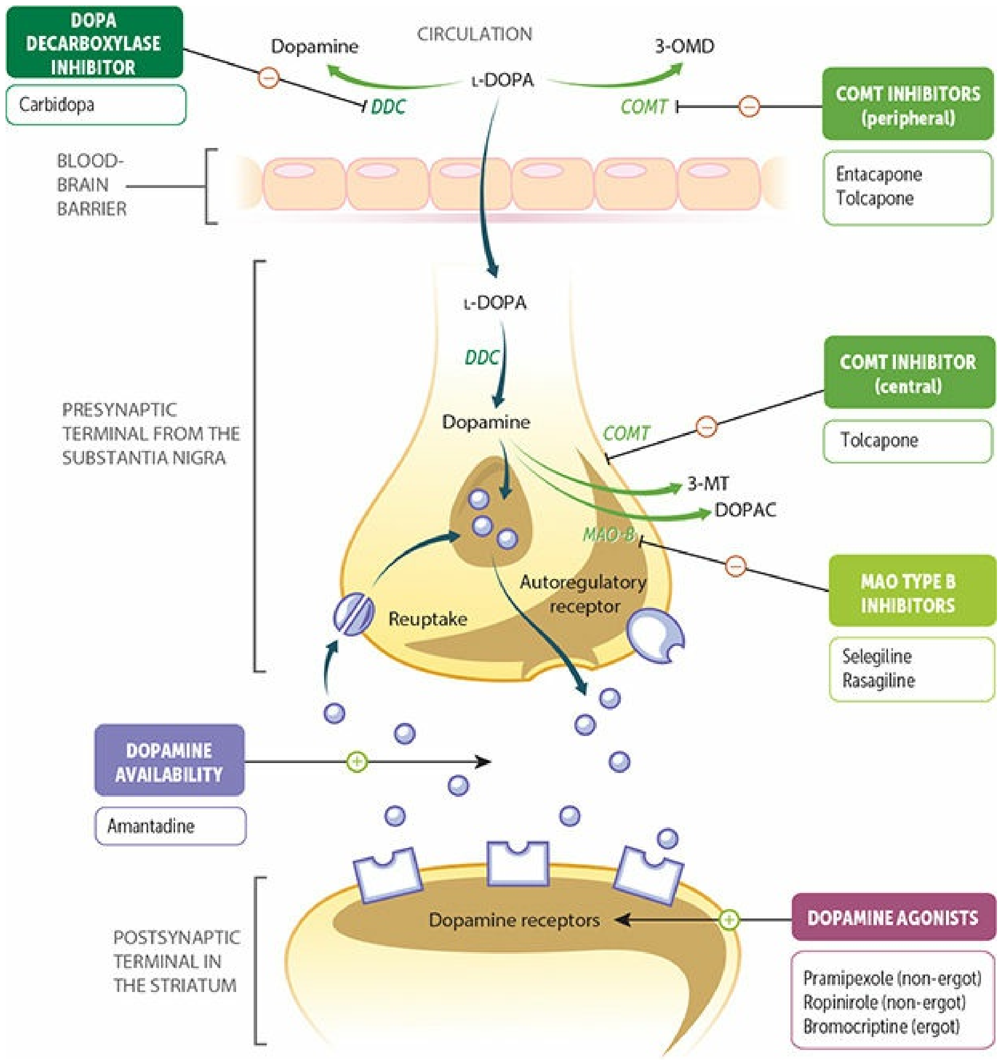
Treatment of Parkinson disease is based on ↑ dopaminergic activity + ↓ cholinergic activity as these circuits become unbalanced with the loss of dopaminergic neurons in the substantia nigra pars compacta.

- Dopamine activates the direct pathway and inhibits the indirect pathway to promote movement.

- Acetylcholine inhibits the direct pathway and activates the indirect pathway to inhibit movement.

Treatment

- **General guidelines:** With the loss of dopaminergic neurons in the substantia nigra pars compacta, cholinergic circuits operate relatively unopposed. Treatment aims to restore balance by ↑ dopaminergic activity + ↓ cholinergic activity (see Fig. 2.9-22). General side effects of agents that ↑ DA activity include nausea/vomiting, orthostatic hypotension, sleepiness, dyskinesias, and confusion/hallucinations. Initial treatment, if possible, involves agents other than levodopa-carbidopa (especially in patients age <65), as long-term use limits utility → "on-off" phenomena.



DOPA DECARBOXYLASE INHIBITOR
Carbidopa
Dopamine
CIRCULATION
L-DOPA
3-OMD
DDC
COMT
COMT INHIBITORS (peripheral)
Entacapone
Tolcapone
BLOOD-BRAIN BARRIER
L-DOPA
DDC
Dopamine
COMT
COMT INHIBITOR (central)
Tolcapone
PRESYNAPTIC TERMINAL FROM THE SUBSTANTIA NIGRA
3-MT
DOPAC
MAO-B
MAO TYPE B INHIBITORS
Selegiline
Rasagiline
Autoregulatory receptor
Reuptake
DOPAMINE AVAILABILITY
Amantadine
Dopamine receptors
DOPAMINE AGONISTS
Pramipexole (non-ergot)
Ropinirole (non-ergot)
Bromocriptine (ergot)
POSTSYNAPTIC TERMINAL IN THE STRIATUM

FIGURE 2.9-22. **Mechanism of action for Parkinson disease drugs.** (Reproduced with permission from USMLE-Rx.com.)

- **Mild symptoms + minimal impact on daily living:**
  - **Initial therapy for any age:** MAO-B inhibitors (selegiline, rasagiline, safinamide) → ↓ MAO-Brain activity → ↑ CNS dopamine, or DA. Tyramine-containing foods (cheese) → hypertensin (HTN) (↓ risk versus MAO-A inhibitors).
  - **Tremor-dominant:** M1 muscarinic ACh receptor antagonists (trihexyphenidyl, benztropine), with cautious use in older adults or amantadine (↑ DA

activity/anticholinergic).

- **Mild to moderate symptoms + impact daily living:**

KEY FACT

In a patient with severe Parkinson disease who develops psychosis, the patient should *not* stop PD medications (this would lead to severe akinesia); instead, the patient should use quetiapine (which is the antipsychotic with the least amount of movement side effects—it's "quiet").

  - **Best therapy:** Nonergot DA receptor agonists (pramipexole, ropinirole, rotigotine) → useful as monotherapy in younger patients (age <65).
- **Moderate to severe symptoms + significant impact on daily living:**
  - **Best and most effective therapy at any age:** Levodopa-carbidopa. Typically, it is the first-line treatment in patients age >65 years. Carbidopa blocks peripheral dihydroxyphenylalanine (DOPA) decarboxylase → ↑ CNS bioavailability of levodopa + ↓ peripheral adverse effects. Long-term use → ↓ endogenous DA → dependence → "on (increased response, dyskinesias) "on-off" phenomena ("on" = increased response, dyskenesias; "off" = loss of response, akinesias).
  - **Levodopa-carbidopa "boosting agents":** MAO-B inhibitors or COMT inhibitors (↑ CNS bioavailability of DA, lessening "off periods"). COMT inhibitors are only used in combination with levodopa-carbidopa and include entacapone (more common) and tolcapone (hepatotoxic). Istradefylline (adenosine A_2 antagonist) can also be used to ↓ "off" phenomena.
- **Surgery:** Patients refractory to medical treatment and those who develop severe disease or are younger (<40 years old) should be considered for implantation of a deep brain stimulator to suppress neural activity of the subthalamic nucleus/globus pallidus internus.
- **Caution with specific drugs:** Caution using drugs with antidopaminergic activity such as metoclopramide, prochlorperazine, and antipsychotics. Quetiapine is "quiet" and has the least movement side effects of the antipsychotics. It is first line in PD patients who develop psychosis. Pimavanserin is an antipsychotic that inhibits 5-hydroxytryptamine (5HT), not DA, and can also be used.

KEY FACT

Anticholinergic side effects:

Blind as a bat (mydriasis + impaired lens accommodation), mad as a hatter (altered mental status), red as a beet (flushing), hot as a hare (hyperthermia), dry as a bone (dry mucosae + skin), the bowel and bladder lose their tone (organ paralysis), and the heart runs alone (tachycardia).

KEY FACT

Pathology determines phenotype:

- Parkinson disease → loss of dopaminergic neurons in basal ganglia → extrapyramidal motor symptoms.
- Alzheimer disease → loss of cholinergic circuits in cortex/subcortex → dementia.

- Amyotrophic lateral sclerosis → loss of UMNs/LMNs → UMN/LMN signs only.
- Myasthenia gravis → loss of acetylcholine receptor function → fatigability.
- Huntington disease → loss of GABA/ACh activity in degenerated cerebrum + striatum → unbalanced dopamine activity → motor, memory, and mood findings.

KEY FACT

If a 55-year-old man presents with slowly progressive weakness with increased reflexes in his left upper extremity and later in his right (upper motor neuron signs) associated with fasciculations and atrophy (lower motor neuron signs) but without bladder disturbance and with a normal cervical MRI, think amyotrophic lateral sclerosis.

AMYOTROPHIC LATERAL SCLEROSIS

Also known as "Lou Gehrig disease" and "motor neuron disease," amyotrophic lateral sclerosis (ALS) is a chronic, progressive disease characterized by loss of upper and lower motor neurons. It is often sporadic (90% of cases) but can also be genetic. Age, family history, and cigarette smoking are risk factors. ALS has an unrelenting course and almost always progresses to respiratory failure and death, usually within 5 years of diagnosis. Men are more commonly affected than women, and onset is generally between 40 and 80 years of age.

History/PE

- Presents with asymmetric, slowly progressive weakness (over months to years) affecting the arms, legs, diaphragm, and lower cranial nerves. Initial presentation is often asymmetric extremity weakness, but can also present with fasciculations (muscle twitching). Weight loss is common.
- Associated with UMN and/or LMN UMN and/or LMN signs (Table 2.9-3).
- Sensation, eye movements, and sphincter tone are generally spared.
- Emotional lability is a common feature.
- Differences in symptom onset and spread cause a variable disease presentation in individuals.

KEY FACT

About 20% of people have "bulbar onset" ALS, which means patients first present with speech and swallowing symptoms (eg, dysarthria, dysphagia, loss of tongue mobility). Patients may also have pseudobulbar affect (sudden inappropriate laughing or crying episodes).

Diagnosis

Diagnosis is usually clinical and follows these criteria:

- Progressive motor dysfunction preceded by previously normal motor function
- Evidence of UMN and LMN involvement in one body segment *or* evidence of LMN involvement in at least two body segments

- Investigations excluding other diseases that explain these symptoms
- EMG/nerve conduction studies revealing widespread denervation and spontaneous action potentials (fibrillation potentials). Such studies are principally performed to exclude other demyelinating motor neuropathies
- CT/MRI of the cervical spine often performed to exclude structural lesions, such as cervical spondylosis with compressive myelopathy. Especially useful in those without bulbar involvement

KEY FACT

Bulbar involvement (involvement of the tongue [CN XII] or oropharyngeal muscles [CN IX, X]) suggests pathology above the foramen magnum, which distinguishes ALS from cervical spondylosis with compressive myelopathy as the cause of symptoms.

Treatment

- Supportive measures and patient education.
- Baclofen can be used for spasticity
- Serial pulmonary assessments beginning at diagnosis. Patients with ALS most commonly die from respiratory failure. First-line treatment for respiratory insufficiency is noninvasive positive-pressure ventilation (PPV).
- Supportive measures and patient education. Riluzole may delay disease progression by 2–3 months by decreasing glutamate-induced excitotoxicity. Edaravone, although new, is a medication used for advanced ALS.

RESTLESS LEGS SYNDROME

- ***Hx/PE:*** A common disorder characterized by leg dysesthesias (abnormal sensations of crawling/itching) and an irresistible urge to move the legs when at rest, especially when lying flat. These symptoms are partially relieved with movement, and they typically occur with inactivity, classically in the evening/night at bedtime and while sleeping (bed partner may report being kicked at night).
- ***Causes:*** Classified as primary (idiopathic) or secondary if it occurs in association with the following conditions: iron-deficiency anemia (misuse of iron in CNS → impairs CNS dopaminergic pathways), located near circadian control centers), uremia (end-stage renal disease [ESRD]/chronic kidney disease [CKD]), cancer (especially colon cancer), pregnancy, diabetes, MS, PD, drugs (eg, antidepressants, metoclopramide).
- ***Dx:*** Clinical + serum iron studies in all patients.
- ***Tx:***
  - Iron supplementation with deficient or low to normal serum ferritin (≤75µg/L)
  - If symptoms are mild/intermittent: Addition of supportive measures (leg massage, heating pads, exercise) + avoid aggravating factors (caffeine, sleep deprivations, certain medications)
  - If symptoms are persistent/moderate to severe: Dopamine agonists (pramipexole, ropinirole); neuropathic pain agents (gabapentin, pregabalin)

KEY FACT

Lesions to the superior colliculus can result in Parinaud syndrome: paralysis of conjugate vertical gaze.

TREMORS

A tremor is an involuntary, rhythmic, oscillatory movement of one or more parts of the body. Tremors represent a diverse set of movement disorders as Figure 2.9-23 and Table 2.9-20 explore.

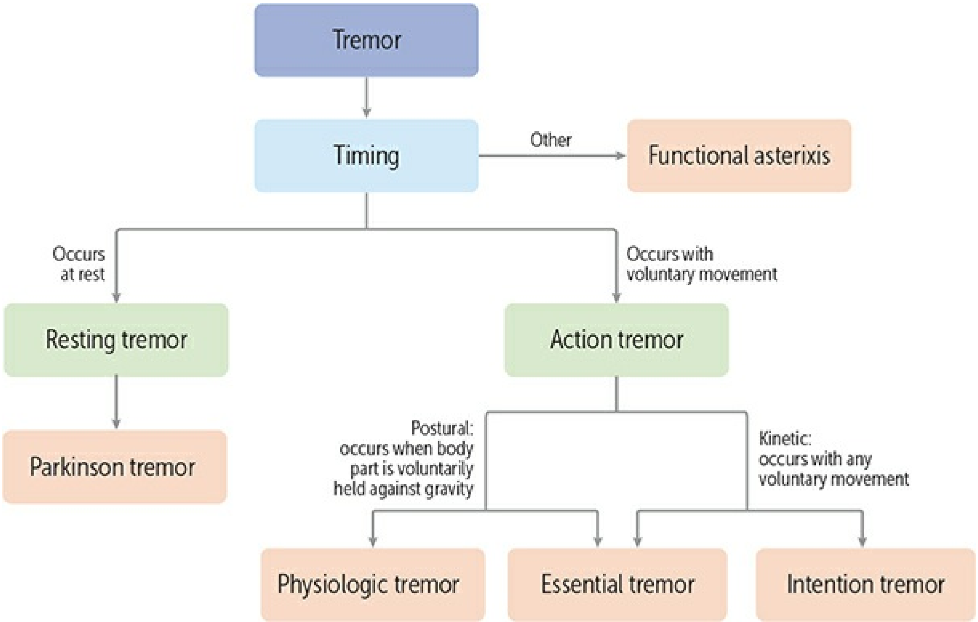

Tremor
Timing
Other
Functional asterixis
Occurs at rest
Occurs with voluntary movement
Resting tremor
Action tremor
Parkinson tremor
Postural: occurs when body part is voluntarily held against gravity
Kinetic: occurs with any voluntary movement
Physiologic tremor
Essential tremor
Intention tremor

FIGURE 2.9-23. **Tremor workup.** (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.9-20. **Classification of Tremors**

TREMOR TYPE	TREMOR SUBTYPE	FEATURES	ETIOLOGIES	IMPROVE	TREATMENT
Resting tremor Occurs without movement (rest)	**Parkinsonian tremor** **"Rest in the park"**	Unilateral "pill-rolling" tremor (4–6 Hz) occurring at rest	PD or neuroleptics	Action (movement)	Dopaminergic / anticholinergic agents
Action tremor Occurs with voluntary movement (action)	**Postural tremor** Occurs when appendage is voluntarily held against gravity	**Physiologic tremor** Bilateral, fine (10–12 Hz)	↑ sympathetic activity	↓ sympathetic activity	Treat cause (anxiety, glucose)
	Kinetic tremor Occurs with any voluntary movement	**Essential tremor "Benign familial tremor"** Bilateral, fine (6–12 Hz), worsens by certain postures (outstretched hands) + voluntary movement (kinetic)	Familial (AD inheritance)	Alcohol + no action (rest)	Propranolol + primidone
		Intention tremor Asymmetrical, coarse (2–4 Hz), worsens as hand approaches target (intention) → zigzag motion → overshoots/undershoots target = dysmetria on finger-to-nose testing	Cerebellar outflow disease	No action (rest)	Cerebellar disease causes
Other	**"Flapping tremor": Asterixis** ***Negative myoclonus***	Bilateral; variable frequency/amplitude; asynchronous inability to maintain outstretched hand posture → loss of tone → involuntary corrective reflex movement = "flapping hand tremor"	↑ ammonia (renal causes; hepatic encephalopathy = "liver flap")	↓ ammonia	Underlying renal/liver cause(s)
	Functional "psychogenic" tremor	Changing, multiple tremor types; abrupt onset; observation worsens; no known neurologic cause	Psychogenic (history of trauma)	Distraction	Psychotherapy

WILSON DISEASE OR HEPATOLENTICULAR DEGENERATION

This is an autosomal recessive disorder that leads to accumulation of copper in various tissues. Mutation in intracellular copper transporter *ATP7B* leads to impaired biliary copper excretion and accumulation of copper in the liver, brain, kidneys, and cornea.

Clinical Features

Patients usually develop liver disease before 40 years of age: jaundice, hepatitis, ascites, and cirrhosis. Associated neurologic disease (eg, dysarthria, dystonia, tremor, parkinsonism) may manifest early in the course of the disease. Proximal tubular dysfunction leading to Fanconi syndrome can present with glucosuria, aminoaciduria, hypouricemia, and proximal renal tubular acidosis. Kayser-Fleischer rings due to copper deposition in the Descemet membrane of the peripheral cornea may be noted on slit-lamp examination.

Q

A 65-year-old man presents to his internist with 10 years of bilateral hand tremors. His mother and older brother have similar tremors. He denies difficulty concentrating, trouble with rising from seated positions, or recent falls. What is the most likely diagnosis?

Diagnosis

- **Initial test:** LFT (look for aspartate aminotransferase [AST]: alanine aminotransferase [ALT] ratio >2); CBC (look for anemia).
- **Diagnostic test:** Ceruloplasmin level (<20 mg/dL) and urinary copper levels (>100 mcg/dL) with Kayser-Fleischer rings confirm diagnosis.
- **Most specific test:** Liver biopsy.

Treatment

Penicillamine is commonly used for chelation, but trientine has fewer side effects. Oral zinc can also be considered as an alternative. A diet low in copper with avoidance of mushrooms, chocolate, nuts, dried fruit, liver, and shellfish is generally advised.

A

Essential tremor ("benign familial tremor") is the most likely diagnosis. Unlike the unilateral resting tremor generally seen in Parkinson disease that improves with movement, essential tremors are usually bilateral action tremors that are worsened by movements. Understand that unilateral tremors are classic for Parkinson disease but can progress to bilateral tremors with other motor symptoms (not present in patient history). Patients classically self-medicate essential tremors with alcohol. First-line treatment of essential tremors is with propranolol or primidone.

NEOPLASMS

Intracranial neoplasms may be primary (30%) or metastatic (70%).

- Of all primary brain tumors, 40% are benign, and these rarely spread beyond the CNS.
- Metastatic tumors are most often from primary lung, breast, kidney, and GI tract neoplasms and melanoma. They occur at the gray-white junction; may be multiple discrete nodules; and are characterized by rapid growth, invasiveness, necrosis, and neovascularization.
- Neoplasms are more common in males than in females, except for meningiomas.

KEY FACT

Most CNS tumors are metastatic. The most common primary CNS tumors in adults are glioblastoma multiforme and meningiomas. The most common primary CNS tumors in children are astrocytomas, followed by medulloblastomas.

History/PE

- Symptoms depend on tumor type and location (see Table 2.9-21), local growth and resulting mass effect, cerebral edema, or ↑ ICP secondary to ventricular obstruction.

TABLE 2.9-21. **Common Primary Neoplasms in Adults**

TUMOR AND APPEARANCE	BENIGN VS MALIGNANT	PRESENTATION	TREATMENT
Astrocytoma (diffuse, anaplastic, grade IV/glioblastoma) Histology shows astrocyte origin with glial fibrillary acid protein (GFAP) ⊕ staining (Image A). "Pseudopalisading" pleomorphic tumor cells border central areas of necrosis, hemorrhage, and/or microvascular proliferation. It is associated with amplification.	Low grade: diffuse—benign, or high grade Anaplastic: malignant Glioblastoma: malignant	Presentation of astrocytomas depends on location of tumor. Some symptoms include headache, seizures, or focal deficits. Glioblastoma is the most common malignant primary brain tumor. It progresses rapidly and has a poor prognosis (<1 year from time of diagnosis).	Surgical removal/resection Radiation and chemotherapy have variable results
Oligodendroglioma MRI brain reveals a mass in the left frontal lobe Histologically has appearance of "fried egg" cells (Image C)—round nuclei with clear cytoplasm. There is a "chicken-wire" capillary pattern.	Low grade: benign, slow growing High grade: anaplastic oligodendroglioma	Oligodendroglioma most commonly presents as seizures, but may be silent. Age of onset is usually between 25 and 45 years. It is most often in frontal lobes and is commonly calcified.	Surgical resection is followed by radiation and chemotherapy, as these tumors are often very chemosensitive.
Meningioma MRI brain reveals a meningioma with associated dural tails. Histology shows spindle cells (Image D), which are concentrically arranged in a whorled pattern, as well as psammoma bodies (laminated calcifications).	Generally benign	Presentation depends on location. Meningioma is often related to cranial neuropathy or is an incidental finding. A classic imaging finding is extension of the tumor along the dura known as a dural tail. The origin of the meningioma is an arachnoid cell.	Surgical resection; radiation for unresectable tumors
Hemangioblastoma MRI brain reveals a hemangioblastoma (Image E, *white arrow*). Histologically has closely arranged, thin-walled capillaries and minimal intervening parenchyma (Image F).	Generally benign	A hemangioblastoma is most often cerebellar. It is associated with von Hippel-Lindau syndrome when found with retinal angiomas. It can produce erythropoietin → secondary polycythemia.	Surgical resection; radiation therapy is sometimes used in recurrent cases.
Pituitary adenoma MRI of the brain revealing mass in the pituitary gland (Image G) Histology shows hyperplasia of only one type of endocrine cells found in pituitary.	Generally benign	May be nonfunctioning (silent) or hyperfunctioning (hormone producing). Nonfunctional tumors present with mass effect (eg, bitemporal hemianopia) due to pressure on optic chiasm. Pituitary apoplexy hyperpituitarism or hypopituitarism is present. Prolactinoma classically presents as galactorrhea, amenorrhea, ↓ bone density due to suppression of estrogen in females and ↓ libido, infertility in males.	Workup for suspected pituitary adenoma includes brain MRI with gadolinium contrast and measurements of serum prolactin, IGF-1, ACTH, and 24-hour urinary free cortisol. Additional tests for TSH, LH, and FSH are obtained based on clinical presentation.

TUMOR AND APPEARANCE	BENIGN VS MALIGNANT	PRESENTATION	TREATMENT
		Most commonly from lactotrophs (prolactin-producing cells), which cause hyperprolactinemia. Less commonly, from somatotrophs (GH-producing cells) → acromegaly, gigantism; corticotrophs (ACTH-producing cells) → Cushing disease. Rarely, from thyrotrophs (TSH-producing cells), gonadotrophs (FSH-, LH-producing cells).	Lactotroph adenomas are initially managed using dopamine agonists (eg, bromocriptine, cabergoline), while most other subtypes require transsphenoidal resection.
Vestibular schwannoma (also known as acoustic neuroma) Head CT reveals a vestibular schwannoma (Image H, *red arrows*). Schwann cell origin, S-100 ⊕. Biphasic, dense, hypercellular areas containing spindle cells alternating with hypocellular, myxoid areas.	Generally benign	Classically at the cerebellopontine angle. Early—compresses CN VIII, VII. Late—can compress CNs V, IX, X. Cranial nerve compression may cause facial numbness, weakness, unilateral hearing loss, tinnitus, vertigo, and loss of balance. Vestibular schwannomas are bilateral in NF2.	Surgical resection, focal radiation, or monitoring

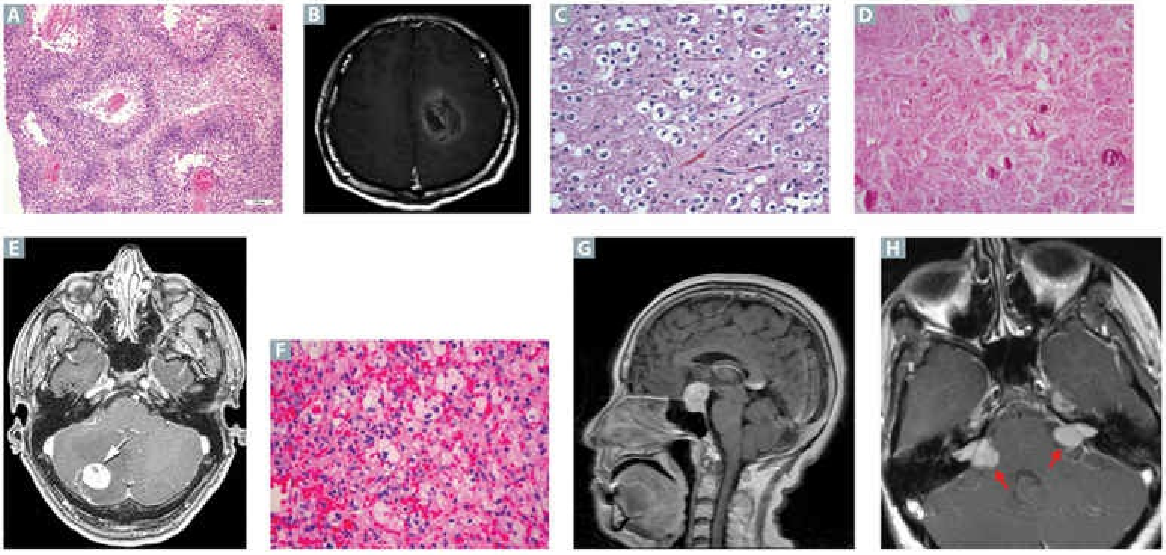


Image A reproduced with permission from Lim SM, Choi J, Chang JH, et al. Lack of ROS1 Gene Rearrangement in Glioblastoma Multiforme. *PLoS One*. 2015;10(9):e0137678. doi:10.1371/journal.pone.0137678. Image B reproduced with permission from Kao HW, Chiang SW, Chung HW, et al. Advanced MR imaging of gliomas: an update. *Biomed Res Int*. 2013;2013:970586. doi:10.1155/2013/970586. Image E reproduced with permission from Park DM, Zhuang Z, Chen L, et al. von Hippel-Lindau disease-associated hemangioblastomas are derived from embryologic multipotent cells. *PLoS Med*. 2007;4(2):e60. doi:10.1371/journal.pmed.0040060. Image F reproduced with permission from Zywicke H, Palmer CA, Vaphiades MS, Riley KO. Optic nerve hemangioblastoma: a case report. *Case Rep Pathol*. 2012;2012:915408. doi:10.1155/2012/915408. Image G reproduced with permission from Wang CS, Yeh TC, Wu TC, Yeh CH. Pituitary macroadenoma co-existent with supraclinoid internal carotid artery cerebral aneurysm: a case report and review of the literature. *Cases J*. 2009;2:6459. doi:10.4076/1757-1626-2-6459. Images C, D, and H reproduced with permission from USMLE-Rx.com.

- Seizures or slowly progressive focal motor deficits are the most common presenting features.
- Although headaches are often thought of as the main presenting symptom, only 31% of patients present with headache at diagnosis, and only 8% have headache as the sole presenting feature.
- When ↑ ICP is the presenting feature, symptoms include headache, nausea/vomiting, and diplopia (false localizing CN VI palsies). In the era of neuroimaging, it is relatively rare for patients to present with ↑ ICP.
- **Other presenting symptoms:** Visual field abnormalities, neurologic deficits, psychiatric

symptoms.

MNEMONIC

Most common cancers that metastasize to the brain—

Lung and Skin Go to the BRain

Lung
Skin
GI
Breast
Renal

Diagnosis

- **Best initial test:** CT and MRI with and without contrast to localize and determine the extent of the lesion.
  - Gadolinium-enhanced MRI is generally better for visualizing soft tissue tumors and vascularity.
  - CT is preferred for evaluating skull base lesions and for emergencies (eg, obstructive hydrocephalus) when an MRI cannot be rapidly acquired.
- Histologic diagnosis via CT-guided biopsy or surgical biopsy.

KEY FACT

Two thirds of primary brain tumors in adults are supratentorial. One third of those in children are supratentorial.

Treatment

- Consider resection (if possible), radiation, and chemotherapy after appropriate consultation with medical and surgical oncology teams.
- Therapy is highly dependent on tumor type, histology, progression, and site (see Table 2.9-21).
- If ICP is ↑, management of ICP calls for the following:
  - Head elevation (↑ venous outflow from brain)
  - Hyperventilation (↓ CO_2 leads to cerebral vasoconstriction resulting in ↓ vasogenic edema)
  - Corticosteroids (↓ vasogenic edema)
  - Mannitol and hypertonic saline (extraction of free water from brain via osmotic diuresis)
  - Removal of CSF
- Automated external defibrillators (AEDs) can be used in patients who have had a seizure.

KEY FACT

Symptoms of ↑ ICP:

- Nausea
- Vomiting
- Diplopia
- Headache that is worse in the morning, with bending over, or with recumbency

NEUROCUTANEOUS DISORDERS

NEUROFIBROMATOSIS

The most common neurocutaneous disorder. There are two major types: neurofibromatosis 1 (NF1, or von Recklinghausen syndrome) and neurofibromatosis 2 (NF2). Both are autosomal dominant diseases caused by mutations to tumor suppressor genes.

History/PE

Diagnostic criteria for NF1 include two or more of the following:

1. Six café au lait spots (flat, uniformly hyperpigmented macules).
2. Two neurofibromas (benign peripheral nerve sheath tumors) of any type (see Fig. 2.9-24).

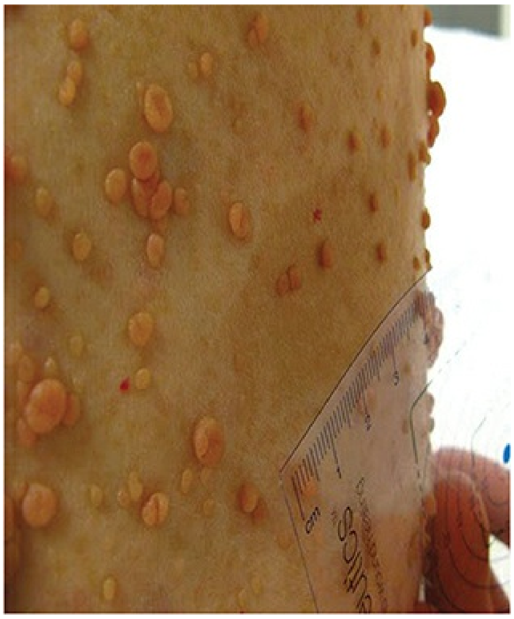


FIGURE 2.9-24. **Neurofibromas associated with neurofibromatosis.** (Reproduced with permission from USMLE-Rx.com.)

3. Freckling in the axillary or inguinal area.
4. Optic glioma (mainly patients under age 6 years).
5. Two Lisch nodules (pigmented iris hamartomas). These are the most specific clinical features of NF1.
6. Bone abnormality (eg, kyphoscoliosis).
7. A first-degree relative with NF1.

Diagnostic criteria for NF2 are as follows:

- Bilateral vestibular schwannomas (also known as acoustic neuromas)
- First-degree relative with NF2 and either:
  - Unilateral acoustic neuromas, or
  - Two of any of the following tumor types: neurofibroma, meningioma, glioma, or schwannoma
- Other features, including seizures, skin nodules, and café au lait spots

Diagnosis

- Usually clinical.
- MRI of the brain, brainstem, and spine with gadolinium.
- A complete dermatologic examination, ophthalmologic examination, bone evaluation, and family history. Auditory testing is recommended. Genetic testing is often not required for diagnosis.
- Evaluation for renal artery stenosis. Patients with NF1 are at increased risk of hypertension due to renovascular lesions, developing as early as childhood.
- Carefully screen patients under age of 6 years for optic nerve glioma.

KEY FACT

Vestibular schwannomas (also known as acoustic neuromas) present with ipsilateral tinnitus, hearing loss, and vertigo. The treatment of choice is surgical resection.

Treatment

- There is no cure; treatment is symptomatic (eg, surgery for kyphoscoliosis or debulking of tumors).
- Vestibular schwannomas (see Table 2.9-21) and optic gliomas can be treated with surgery or radiosurgery. Rapidly growing meningiomas can be resected.
- Mutation in NF1 tumor suppressor gene causes increased signal transduction through the Ras/Raf/MEK/MAPK pathway. Use of MEK or MAPK inhibitors (ie, selumetinib) can be used to induce tumor regression.

TUBEROUS SCLEROSIS

Autosomal dominant disorder that affects many organ systems, including the CNS, skin, heart, retina, lungs, and kidneys. A mutation in the tuberous sclerosis complex (TSC) gene leads to this disorder. *TSC1* codes for the tumor suppressor gene hamartin, and *TSC2* codes for the tumor suppressor gene tuberin. Mutations in *TSC2* are more common than in *TSC1*.

History/PE

- Seizures are the most frequent presenting symptom, with infantile spasms being the most common type. Tuberous sclerosis also presents with “ash-leaf” hypopigmented lesions (Fig. 2.9-25A) on the trunk and extremities and with mental disability (↑ likelihood with early age of onset).

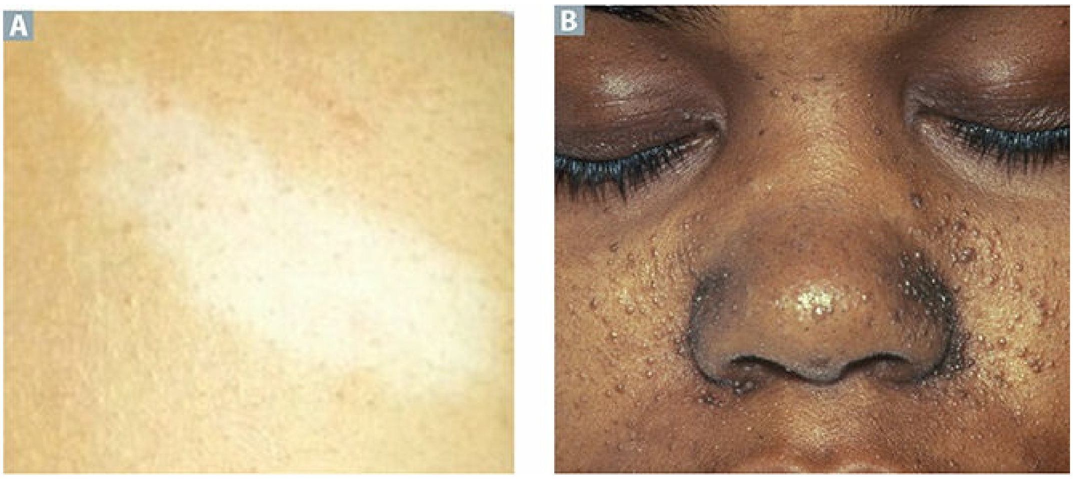


FIGURE 2.9-25. Tuberous sclerosis. (A) "Ash-leaf" macules on a patient with tuberous sclerosis and **(B)** angiofibromas in a butterfly distribution. (Image A reproduced with permission from Falsafi P, Taghavi-Zenouz A, Khorshidi-Khiyavi R, et al A case of tuberous sclerosis without multiorgan involvement. *Glob J Health Sci.* 2015 Feb 24;7(5):124-31. doi: 10.5539/gjhs.v7n5p124. Image B adapted with permission from Fred H, van Dijk H. Images of memorable cases: Case 143. Connexions Website. December 4, 2008. Available at: http://cnx.org/content/m14923/1.3/.)

- Other skin manifestations include angiofibromas (small red nodules on the nose and cheeks in the distribution of a butterfly Fig. 2.9-25B), shagreen patch (a rough papule in the lumbosacral region with an orange-peel consistency), and periungual fibromas.
- Other symptoms are secondary to small benign tumors that grow on the face, eyes, brain, kidney, and other organs. For example:
  - Congestive heart failure (CHF) from cardiac rhabdomyoma; renal disease from renal cysts, angiomyolipomas, or carcinomas
  - Developmental disability from brain lesions (eg, subependymal nodules)
- Lymphangioleiomyomatosis (LAM) is cystic lung disease that is also due to a mutation in the TSC. LAM can present as a late manifestation of tuberous sclerosis, often in the third or fourth decade, or it can occur sporadically. Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, has been found to slow disease progression.

KEY FACT

Infantile spasms occur in children <3 years of age and can consist of head bobbing, flexor spasms, extensor spasms, or movements that mimic the startle response. They may be associated with psychomotor regression or behavioral changes.

Diagnosis

- Usually clinical
- Ash-leaf lesions enhanced by a Wood's ultraviolet (UV) light lamp
- **Imaging:**
  - **MRI of brain:** Evaluate for subependymal giant cell astrocytoma and calcified tubers (potato-like nodules) within the cerebrum in the periventricular area. If lesions obstruct CSF outflow, obstructive hydrocephalus can develop.
  - **Ophthalmic exam:** Evaluate for retinal hamartomas and eyelid angiofibromas.
  - **Echocardiography:** Evaluate for rhabdomyoma of the heart, especially in the apex of the left ventricle (affects >50% of patients).

  - **MRI of abdomen:** Evaluate for renal disease (cysts, angiomyolipoma, and/or carcinoma).
- **EEG:** Evaluate for seizure activity.

Treatment

- Treatment should be based on symptoms (eg, cosmetic surgery for facial sebaceous adenomas).
- Seizures should be treated.
  - When standard epileptic medications fail, mTOR inhibitors (eg, everolimus) can help reduce seizures.
  - If infantile spasms are present, first-line treatment is with vigabatrin, which enhances GABA transmission. Adrenocorticotropic hormone (ACTH) can be used as an alternative/adjunctive.
- Surgical intervention may be indicated in the setting of ↑ ICP from obstructive hydrocephalus or for seizures associated with an epileptogenic focus or severe developmental delay.

STURGE-WEBER SYNDROME

Sturge-Weber syndrome is due to a somatic mosaic mutation in the *GNAQ* gene, and therefore is not an inheritable disease.

History/PE

Facial capillary malformation (port wine stain) is usually in a V1 distribution. This finding in isolation does not qualify for the diagnosis of Sturge-Weber syndrome since *GNAQ* mutations constitute a spectrum disorder with isolated port wine stain as the mildest form. Twenty percent have a leptomeningeal capillary-venous malformation of the brain and eye that is adjacent to the port wine stain and are thus diagnosed as having Sturge-Weber syndrome. The brain parenchyma may be atrophic and contain calcific deposits. Seizures, strokelike episodes, hemiparesis, and mental retardation commonly occur.

Diagnosis

Preferred diagnostic test is brain MRI with contrast. The image may reveal intracranial calcifications that resemble a “tramline.”

Treatment

- Photothermolysis can be used for treatment of port wine stains.
- Low-dose aspirin beginning in infancy may decrease the frequency and duration of seizures.
- Anticonvulsant medications are first line for management of seizures.

VON HIPPLE-LINDAU SYNDROME

Von Hipple-Lindau (VHL) syndrome is an inherited autosomal dominant condition characterized by the presence of benign and malignant tumors in many organ systems, including the retina, CNS, pancreas, kidneys, and adrenals. It is caused by a mutation in the VHL tumor suppressor gene. Patients with type 1 VHL have a very low risk of developing pheochromocytoma, but patients with type II VHL (caused by missense mutations) have a higher risk for pheochromocytoma.

History/PE

- Hemangioblastomas are the hallmark tumors of VHL. When they occur in the CNS, especially the cerebellum and spinal cord, they can cause ataxia and headaches. Retinal hemangioblastomas may cause vision loss, and they are often identified on fundoscopy.
- One half of all cases of pheochromocytomas under the age of 18 years are due to VHL, and they result in episodes of palpitations, hypertension, and sweating.
- Other VHL-associated tumors include:
  - Renal cell carcinoma (clear cell type) and renal cysts
  - Serous cystadenoma of the pancreas
  - Endolymphatic sac tumor
  - Papillary cystadenoma of epididymis and broad ligament
  - Epididymal cysts

Diagnosis

- Genetic testing for individuals with manifestations of VHL disease or family history
- MRI of the brain and spinal cord to evaluate for lesions
- Levels of catecholamines to evaluate for presence of pheochromocytoma
- Complete audiologic exam to evaluate for hearing loss (can be caused by endolymphatic sac tumors)

Treatment

- Routine surveillance of the abdomen can check for renal cell carcinoma, pheochromocytomas, and pancreatic tumors. Annual retinal exams should be done to evaluate for retinal hemangioblastomas.
- For patients with symptomatic hemangioblastomas, surgical intervention should be considered. If unresectable or if there are contraindications to surgery, treatment with belzutifan (hypoxia-inducible factor [HIF]-2 alpha inhibitor) can be considered. In VHL disease, levels of HIF-1A and HIF-2A transcription factors are elevated, causing an increase in physiologic angiogenesis via upregulation of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF).
- Patients with renal cell carcinoma >3 cm should undergo surgical intervention rather than routine surveillance.

ATAXIA-TELANGIECTASIA

Autosomal recessive disease caused by a mutation in the *ATM* gene, which encodes DNA repair enzymes. Leads to aberrant repair of double-stranded DNA breaks, causing cell death (eg, Purkinje cells in the cerebellum are particularly susceptible).

History/PE

- Cerebellar ataxia is often the first presenting symptom in infancy or early childhood. Patients may also present with ocular apraxia (inability to control purposeful eye movements), cognitive impairment, extrapyramidal symptoms, and peripheral neuropathy.
- Telangiectasias are common, most often in the face, eyes, and ears.
- Immune deficiency (especially IgA) predisposes patients to recurrent sinopulmonary infections, which may lead to interstitial lung disease.

- Up to one fourth of patients will develop a malignancy, most often lymphomas or leukemias.

Diagnosis

- Usually clinical, but genetic testing supportive of diagnosis
- Low IgA
- Elevated levels of α-fetoprotein (AFP) often seen
- Imaging studies involving ionizing radiation to be minimized

Treatment

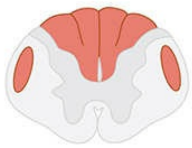
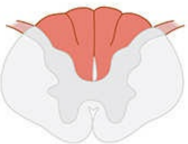
No specific treatment exists for progressive ataxia and cerebellar degeneration. Infections should be treated with antibiotics. Prophylactic antibiotics can be considered.

OTHER NEUROLOGIC DISEASES

NUTRITIONAL DEFICIENCIES

Table 2.9-22 describes neurologic syndromes commonly associated with nutritional deficiencies.

TABLE 2.9-22. **Neurologic Syndromes Associated With Nutritional Deficiencies**

VITAMIN	SYNDROME	SIGNS/SYMPTOMS	CLASSIC PATIENTS	TREATMENT
Thiamine (vitamin B$_1$)	Wernicke encephalopathy	Classic triad consisting of encephalopathy, ophthalmoplegia, and ataxia	Patients with acute/chronic alcohol overuse (toxin effect on cerebellar Purkinje fibers), hyperemesis, starvation, renal dialysis, AIDS. Usually brought on or exacerbated by high-dose glucose administration	Reversible almost immediately with thiamine administration Always give thiamine before glucose
	Korsakoff dementia	Above plus anterograde and retrograde amnesia, horizontal nystagmus, and confabulations	Same as above; usually occurs in Wernicke syndrome that was treated too late or inadequately	Irreversible
Cobalamin (vitamin B$_{12}$)[a] Subacute combined degeneration  Tabes dorsalis 	Peripheral neuropathy; subacute combined degeneration (SCD)	Gradual, progressive gait disorder due to profound loss of proprioception Symmetric paresthesia, stocking-glove sensory neuropathy, leg stiffness, spasticity, paraplegia, bowel and bladder dysfunction, sore tongue, and dementia Associated with elevated methylmalonic acid levels	Patients with pernicious anemia; strict vegetarians; status postgastric or ileal resection; ileal disease (eg, Crohn); patients with acute/chronic alcohol overuse or others with malnutrition	B$_{12}$ injections or large oral doses
Folate[a]	Folate deficiency	Irritability; personality changes without the neurologic symptoms of SCD	Patients with acute/chronic alcohol overuse	Reversible if corrected early

[a] Associated with ↑ homocysteine and an ↑ risk for vascular events. (Images reproduced with permission from USMLE-Rx.com.)

IDIOPATHIC INTRACRANIAL HYPERTENSION

A disorder characterized by raised ICP with neurologic manifestations such as headaches, papilledema (most common), and vision loss, without any indication toward another cause of raised ICP on neuroimaging. The disease has no proven etiology (*idiopathic*), but is believed to be either due to decreased resorption and/or increased production of CSF. Other proposed mechanisms include vascular (transverse sinus stenosis), hormonal (aldosterone excess), and cellular (increased outflow resistance to CSF). Risk factors include female sex, obesity, use of tetracyclines, and hypervitaminosis A.

History/PE

- Patients usually have bilateral, frontal (retrobulbar) headache, more pronounced in the mornings and on Valsalva; transient visual loss; diplopia; pulsatile tinnitus.
- Sixth nerve (abducens) palsy may be a nonlocalizing sign of raised ICP.

Diagnosis

- Neuroimaging (MRI with venography) is preferred to rule out other causes of raised ICP. CT done when MRI contraindicated.

- CSF opening pressure >25 cm H_2O in adults is suggestive of diagnosis.
- Ophthalmologic evaluation is mandatory to rule out papilledema (see Ophthalmology section).

Treatment

- Goals of therapy include alleviation of symptoms and preservation of vision.
- Best first treatment when patients have minimal symptoms is to address risk factors/comorbidities and advise weight loss.
- Carbonic anhydrase inhibitor, acetazolamide, is best first medication to use in these patients.

Q

A 61-year-old man presents to the emergency department with a 6-month history of progressively worsening nausea and morning headache. The patient is in no apparent acute distress. What is the preferred diagnostic study?

- When medical therapy fails, the physician should consider topiramate and serial LPs (not preferred, as CSF reforms within 6 hours) prior to surgery.
- Surgery is advised when patients have worsening visual defects despite medical therapy, and presence of visual acuity loss is secondary to papilledema. Performed procedures include optic nerve sheath fenestration (ONSF) and CSF-shunting procedures.

OPHTHALMOLOGY

VISUAL FIELD DEFECTS

Figure 2.9-26 illustrates common visual field defects and the anatomic areas with which they are associated.

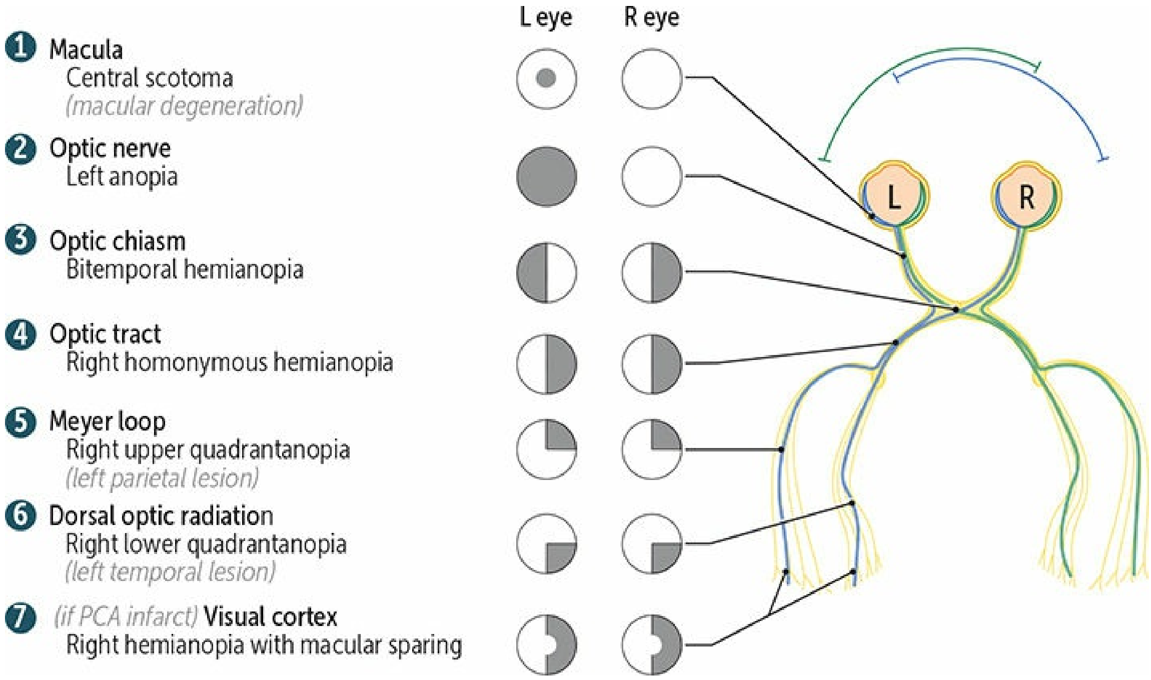

L eye
R eye
① Macula
Central scotoma
(macular degeneration)
② Optic nerve
Left anopia
③ Optic chiasm
Bitemporal hemianopia
④ Optic tract
Right homonymous hemianopia
⑤ Meyer loop
Right upper quadrantanopia
(left parietal lesion)
⑥ Dorsal optic radiation
Right lower quadrantanopia
(left temporal lesion)
⑦ (if PCA infarct) Visual cortex
Right hemianopia with macular sparing
L
R

FIGURE 2.9-26. **CNS lesions cause characteristic visual field defects.** (Reproduced with permission from USMLE-Rx.com.)

HORDEOLUM

Painful abscess of the eyelid, also called a stye, caused by inflammation or infection of a sebaceous gland located around the eyelash (Zeis and Moll) or inner lid margin (meibomian). *S aureus* is the most common pathogen. Hordeolum presents with localized swelling and erythema. Initial management consists of warm, moist compresses, topical antibiotic/steroids ointment, and lid massage several times a day to facilitate drainage. Refractory hordeola may be referred to ophthalmologists for incision and drainage.

CHALAZION

Granulomatous lesion of the eyelid that presents with localized swelling and a nontender, hard nodule. Differentiated from a hordeolum by a comparative lack of erythema and pain. Management includes warm compress, topical antibiotic/steroid combination, and possible incision and drainage (refractory lesions).

A

This patient presents with symptoms that are concerning for increased ICP. As he is not in acute distress, MRI is the preferred study because it is better for visualizing soft tissue and vascularity.

BLEPHARITIS

A chronic inflammatory condition of the eyelash follicles (anterior) or Meibomian glands (posterior) of the eyelid, producing lid irritation that may lead to erythema and pruritis of the eyelid or conjunctiva (Fig. 2.9-27), excessive tear production, eyelash crusting, and light sensitivity. Initial treatment is with warm compresses, lid hygiene, and lubricating drops to prevent corneal dryness. Patients who do not respond to initial therapy are treated with topical erythromycin. Oral antibiotics (doxycycline, azithromycin) may be used for refractory cases. Lid hygiene, including washing, and avoidance of irritants such as smoke, eye makeup, or contact lenses is emphasized to prevent future symptoms.

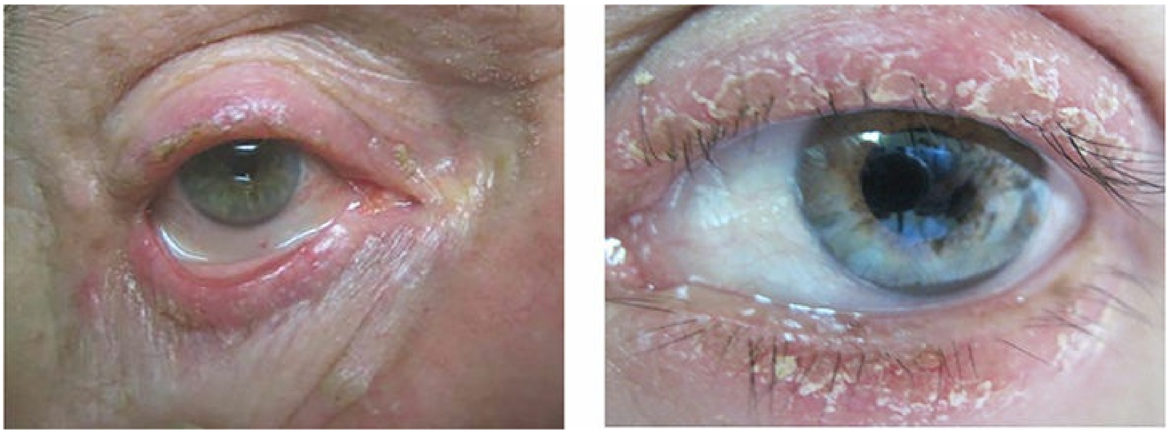


FIGURE 2.9-27. Blepharitis. (Left image reproduced with permission from USMLE-Rx.com. Right image reproduced with permission from Vanzzini Zago V, Alcantara Castro M, Naranjo Tackman R. Support of the laboratory in the diagnosis of fungal ocular infections. *Int J Inflam.* 2012;2012:643104. doi:10.1155/2012/643104.)

CORNEAL ABRASION

Damage to the corneal epithelium (Fig. 2.9-28A) caused by trauma (including from foreign bodies or contact lenses). Patients report severe eye pain, foreign body sensation, and photophobia. Diagnosis is made by fluorescein examination, where there is increased uptake of fluorescein stain in the area of abrasion under a Wood’s lamp (Fig. 2.9-28B). Treatment consists of removing any retained foreign body, pain control, and topical antibiotic therapy. Fluoroquinolone drops are used for contact lens wearers due to risk of *Pseudomonas* infection, whereas erythromycin ointment or polymyxin/trimethoprim drops are suitable for patients who do not wear contact lenses.

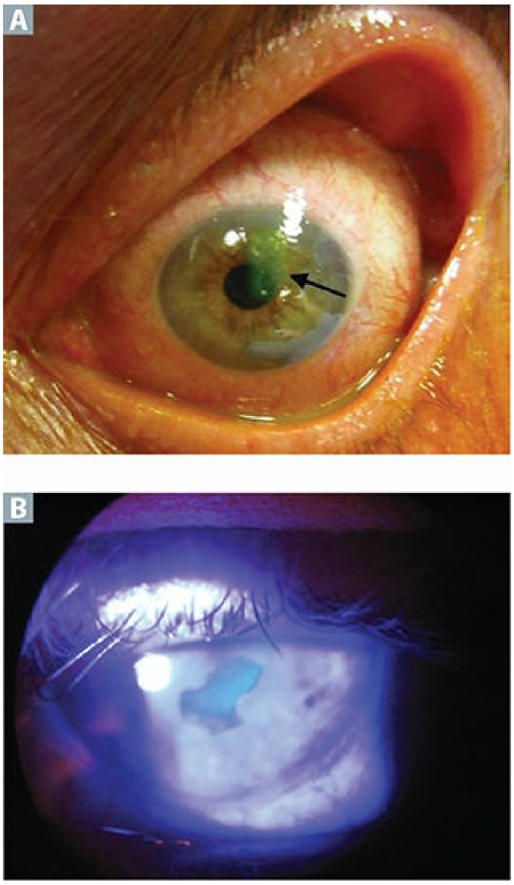


FIGURE 2.9-28. **(A)** Corneal abrasion; **(B)** Wood's lamp examination with corneal abrasion. (Image A reproduced with permission from Gilani CJ, Yang A, Yonkers M, Boysen-Osborn M. Differentiating urgent and emergent causes of acute red eye for the emergency physician. *West J Emerg Med.* 2017;18[3]:509-517. doi:10.5811/westjem.2016.12.31798. Image B reproduced with permission from USMLE-Rx.com.)

PRESEPTAL (PERIORBITAL) CELLULITIS

Infection of the eyelid and surrounding soft tissue anterior to the orbital septum. Presents with painful erythema and edema of the eyelid. *S aureus* is the most common pathogen. Patients with no skin trauma are treated with amoxicillin-clavulanic acid, whereas patients with skin trauma are covered for methicillin-resistant *S aureus* (MRSA) with the addition of trimethoprim-sulfamethoxazole or clindamycin. This condition is differentiated from the more serious orbital (postseptal) cellulitis by lack of ophthalmoplegia, pain with eye movement, or proptosis. CT of the orbit can be used to differentiate the site of infection in unclear cases.

Q

A 24-year-old female with a body mass index (BMI) of 33 presents with a 3-week history of constant retro-orbital headache with occasional nausea, vomiting, and tinnitus. She also developed new-onset diplopia 2 hours before presentation. On physical examination, she is noted to have papilledema. What is the most likely diagnosis, and what are the risk factors for this condition?

ORBITAL (POSTSEPTAL) CELLULITIS

Infection of the ocular muscles or orbital fat, sparing the globe, that may lead to vision loss or death if left untreated. Commonly caused by direct spread of infection from the paranasal sinuses. Other causes include trauma, ophthalmic surgeries, dental infections, and dacryocystitis. It is usually caused by staphylococci (including MRSA), streptococci, and *H influenzae* (in children). In patients with diabetes and immunocompromise, *Mucor* and *Rhizopus* must be included in the differential diagnosis.

KEY FACT

Orbital cellulitis can be distinguished from preseptal cellulitis by the presence of the following clinical features: restricted or painful eye movements, ↓ visual acuity, diplopia, proptosis, and presence of a relative afferent pupillary defect.

History/PE

Presents with acute-onset fever, proptosis, ↓ extraocular movement, ocular pain, and ↓ visual acuity. The physician should look for a history of ocular trauma/surgery or sinusitis. Palatal or nasal mucosal ulceration with coexisting maxillary and/or ethmoid sinusitis suggests mucormycosis or *Rhizopus*.

Diagnosis

Mostly clinical. **Best initial test:** Blood and tissue fluid culture. CT scan or MRI of the orbit and sinuses to rule out orbital abscess and intracranial involvement.

Treatment

- The patient should be admitted and administered broad-spectrum IV antibiotics such as vancomycin and ceftriaxone. Metronidazole is added for intracranial extension; case requires an ophthalmologic/ear, nose, throat (ENT) consult.
- Abscess formation or a worsening condition may necessitate surgery.
- Patients with diabetes or immunocompromise should be treated with amphotericin B and surgical debridement (often associated with cavernous sinus thrombosis) if *Mucor* or *Rhizopus* is diagnosed.

KEY FACT

Neisseria conjunctivitis is an ocular emergency often requiring inpatient parenteral antibiotic therapy.

CONJUNCTIVITIS

Inflammation of the conjunctiva producing a red-appearing eye (Fig. 2.9-30). It is most often allergic, viral, or bacterial but can also be fungal, parasitic, or chemical. It is essential to differentiate potentially vision-threatening infectious etiologies from allergic or other causes of conjunctivitis and to identify other vision-threatening conditions that may mimic conjunctivitis. Table 2.9-23 lists the common etiologies of infectious conjunctivitis.

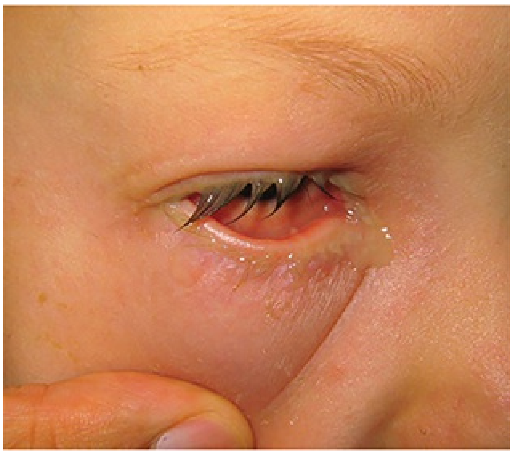


FIGURE 2.9-30. **Conjunctivitis.** (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.9-23. **Common Causes of Infectious Conjunctivitis**

	PATHOGEN	CHARACTERISTICS	DIAGNOSIS	TREATMENT
Bacterial	Staphylococci, streptococci, *Haemophilus, Pseudomonas, Moraxella*	Foreign body sensation, purulent discharge	Gram stain and culture if severe	Antibiotic drops/ointment
	Neisseria gonorrhoeae	An emergency—corneal involvement can lead to perforation and blindness	Gram stain showing gram ⊖ intracellular diplococci	IM or IV ceftriaxone; inpatient treatment if complicated. Contact tracing/treat sexual partners.
	Chlamydia trachomatis A–C Trachoma (global)	Recurrent epithelial keratitis in childhood, trichiasis, corneal scarring, and entropion Leading cause of preventable blindness world wide	Clinical (most often), PCR	Azithromycin (single oral dose) in mass treatment
	Chlamydia trachomatis D–K	Ophthalmia neonatorum: Mucopurulent conjunctivitis in neonates Adult inclusion conjunctivitis: Chronic conjunctivitis with mild mucopurulent discharge in adults	Ophthalmia neonatorum: Giemsa stain, PCR Adult inclusion conjunctivitis: PCR	Ophthalmia neonatorum: Erythromycin (first line), azithromycin Adult inclusion conjunctivitis: Azithromycin (single oral dose), screening for gonorrhea and contact tracing
Viral	Adenovirus (most common)	Copious watery discharge, severe ocular irritation, preauricular lymphadenopathy, pharyngitis (with adenovirus, "pharyngoconjunctival fever") Occurs in epidemics		Contagious; self-limited

- **Allergic conjunctivitis:** Bilateral predominantly itchy eyes. Treat with antihistamine (olopatadine) eye drops.
- **Bacterial conjunctivitis:** Purulent discharge. Treat with erythromycin ointment or fluoroquinolone drops in contact lens wearers.
- **Viral conjunctivitis:** Watery discharge, often bilateral. Self-limiting. Treat with antihistamine (olopatadine) or lubricating eye drops for symptomatic relief.

Given this patient's symptoms and risk factors, she probably has pseudotumor cerebri, also known as idiopathic intracranial hypertension (IIH). In IIH, symptoms are suggestive of a brain tumor, and CSF pressure will be ↑; however, neuroimaging will be normal. Obesity, tetracycline, growth hormone, and excess vitamin A are risk factors for the disease. Treatment is with acetazolamide, topiramate, optic nerve fenestration, and ventriculoperitoneal shunt if needed.

ACUTE DACRYOCYSTITIS

Infection of the lacrimal sac, usually by *Staphylococcus* or *Streptococcus* spp. May progress to orbital cellulitis or meningitis if left untreated. Congenital nasolacrimal duct stenosis and dacryocystocele (nasolacrimal duct cyst) are predisposing conditions.

- ***Hx/PE:*** Presentation with purulent eye discharge, as well as inflammation overlying the lacrimal system and medial eyelids (medial canthal region) (Fig. 2.9-31). Less commonly fever and ↑ WBC.

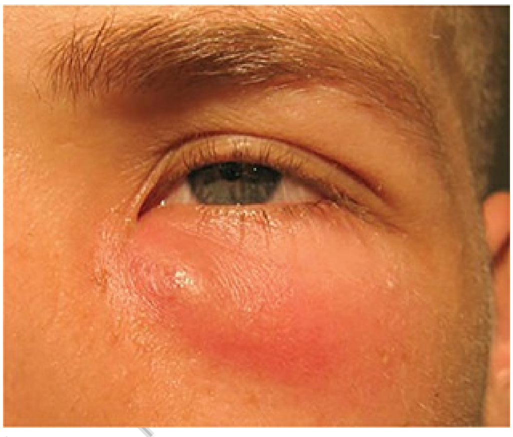


FIGURE 2.9-31. **Dacryocystitis.** (Reproduced with permission from USMLE-Rx.com.)

- ***Dx:*** Clinical diagnosis.
- ***Tx:*** If mild, oral anti-staphylococcus/streptococcus agents. If serious, immediate empiric broad-spectrum antibiotics to prevent orbital cellulitis.

HERPES SIMPLEX KERATITIS

Viral infection of the cornea. Common cause of visual impairment in the United States.

- ***Hx/PE:*** Presents with pain, blurred vision, tearing, and redness. The virus remains dormant along the trigeminal nerve and may reactivate during periods of immunocompromise such as illness.
- ***Dx:*** Typically clinical. However, dendritic ulcers (Fig. 2.9-32) are characteristic. Epithelial scrapings show multinucleated giant cells. PCR of conjunctival/corneal swab for confirmation.

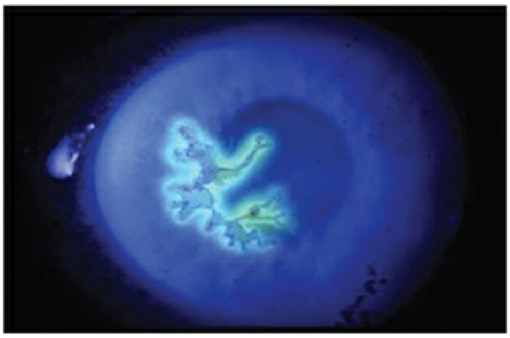


FIGURE 2.9-32. **Herpes simplex keratitis with dendritic ulcer.** (Reproduced with permission from Gilani CJ, Yang A, Yonkers M, Boysen-Osborn M. Differentiating urgent and emergent causes of acute red eye for the emergency physician. *West J Emerg Med.* 2017;18[3]:509-517. doi:10.5811/westjem.2016.12.31798.)

- ***Tx:*** Oral or topical antiviral therapy.

CONTACT LENS KERATITIS

Medical emergency, often caused by *Pseudomonas* infection.

- ***Hx/PE:*** Typically presents with painful, red eye and opacification and ulceration of the cornea. Most patients report a history of improper contact lens hygiene, such as reusing lens solution or showering/swimming with lenses in. Severe disease can cause corneal perforation and permanent vision loss.
- ***Dx:*** Clinical. Corneal scrape and bacterial culture are usually performed for antibiotic sensitivity.
- ***Tx:*** Immediate removal of the contact lens and administration of topical broad-spectrum antibiotics.

UVEITIS

Infectious or noninfectious inflammation of the uvea—specific name is based on location within the affected eye. Anterior uveitis: iritis; posterior uveitis: choroiditis and/or retinitis. Associated with systemic inflammatory disorders (eg, sarcoidosis, inflammatory bowel disease, rheumatoid arthritis, juvenile idiopathic arthritis, human leukocyte antigen (HLA)-B27–associated conditions)

History/PE

- Patients with anterior uveitis may have pain and redness of the eye—often worse at the limbus (corneal-scleral junction) (Fig. 2.9-33). They may have hypopyon (accumulation of pus in anterior chamber).

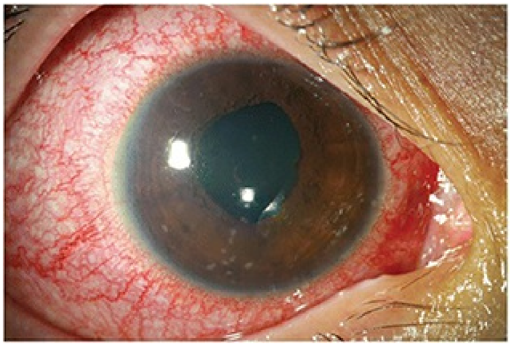


FIGURE 2.9-33. **Uveitis.** (Reproduced with permission from Barut K, Rzayev T, Canpolat N, et al. Acute granulomatous

iridocyclitis in a child with tubulointerstitial nephritis and uveitis syndrome. *J Ophthalmic Inflamm Infect.* 2015;5:3. Published 2015 Feb 13. doi:10.1186/s12348-015-0035-2.

- Posterior uveitis presents with visual changes such as decreased visual acuity or floaters in the visual fields.

Diagnosis

Diagnosis is made by slitlamp examination showing leukocytes in the anterior chamber, vitreous humor, or other signs of inflammation of the retina.

Treatment

- Treatment of infectious uveitis is targeted toward the specific pathogen.
- Noninfectious uveitis is treated with topical glucocorticoids. Oral or intraocular glucocorticoids are used for refractory cases.

REFRACTIVE ERRORS

Common cause of impaired vision, correctable with glasses, contact lenses, or refractive surgery.

- **Hyperopia,** also called “farsightedness.” Eye too short for refractive power of cornea and lens → light focused behind retina. Correct with convex (converging) lenses.
- **Myopia,** also called “nearsightedness.” Eye too long for refractive power of cornea and lens → light focused in front of retina. Correct with concave (diverging) lens.
- **Astigmatism,** irregular curvature of cornea → different refractive power at different axes. Correct with cylindrical lens.

PRESBYOPIA

Aging-related impaired accommodation (focusing on near objects), primarily due to ↓ lens elasticity, changes in lens curvature, and ↓ strength of the ciliary muscle. Patients often need “reading glasses” (magnifiers).

GLAUCOMA

In the eye, aqueous humor produced by the ciliary body behind the iris travels through the pupil into the anterior chamber and is then drained back into the bloodstream via the trabecular meshwork in the angle of the anterior chamber.

KEY FACT

Closed-angle glaucoma headaches are triggered by darkness (caused by pupillary dilation). Migraine headaches are triggered by bright lights.

KEY FACT

Open-angle glaucoma generally occurs bilaterally, but closed-angle glaucoma usually presents unilaterally.

- Any process that disrupts this natural flow (Fig. 2.9-34) can ↑ intraocular pressure (IOP), damaging the optic nerve head and causing visual field deficits. Glaucoma is the result of such damage to the nerve.

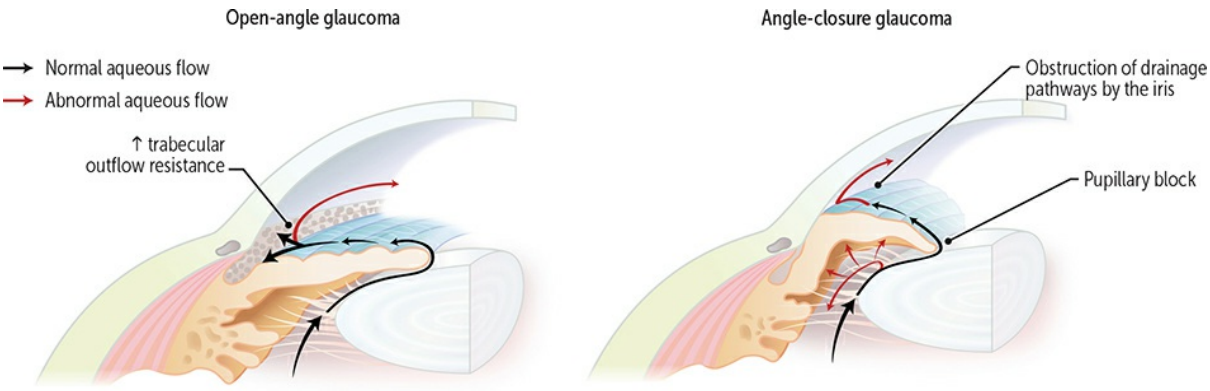

Open-angle glaucoma
Angle-closure glaucoma
Normal aqueous flow
Abnormal aqueous flow
↑ trabecular outflow resistance
Obstruction of drainage pathways by the iris
Pupillary block

FIGURE 2.9-34. **Aqueous humor flow in glaucoma.** (Reproduced with permission from USMLE-Rx.com.)

- Open-angle glaucoma is much more common in the United States than closed-angle glaucoma (see Fig. 2.9-35 and Table 2.9-24).

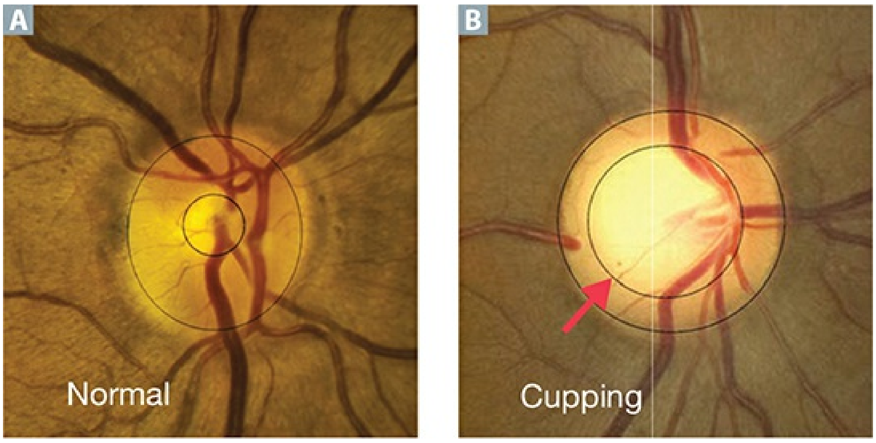

A
Normal
B
Cupping

FIGURE 2.9-35. **Findings in open- and closed-angle glaucoma. (A)** Normal optic disc. **(B)** Cupping (increased cup-to-disc ratio) seen in open-angle glaucoma. (Reproduced with permission from EyeRounds.)

TABLE 2.9-24. **Closed-Angle vs Open-Angle Glaucoma**

	CLOSED-ANGLE GLAUCOMA	OPEN-ANGLE GLAUCOMA
Etiology	Disrupted flow of aqueous humor into the anterior chamber results in ↑ pressure in the posterior chamber, leading to angle closure that ↓ drainage. This ophthalmic emergency can cause blindness. Although this disease usually presents unilaterally, it often affects both eyes sequentially.	Diseased trabecular meshwork results in ↓ drainage, leading to gradual ↑ in IOP and progressive vision loss.
Risk factors	Family history, older age (55–70 years), Asian descent, hyperopia, prolonged pupillary dilation (prolonged time in a dark area, stress, medications), anterior uveitis, and lens dislocation.	Age >40 years, family history of open-angle glaucoma, Black ethnicity, diabetes, and myopia.
History/PE	Extreme, sudden-onset eye pain, blurred vision, headache, nausea, and vomiting. A hard, red eye is seen; the pupil is dilated and nonreactive to light.	Usually asymptomatic until late in the clinical course, when it can cause gradual loss of peripheral vision if left untreated. Cupping of the optic nerve head is seen on funduscopic exam.
Diagnosis	**Best initial test:** Ocular tonometry (to measure IOP) can quickly provide additional information. **Best diagnostic test:** Assessing the corneal angle with gonioscopy is the gold standard.	**Best initial test:** Tonometry. **Best diagnostic test:** Ophthalmoscopic visualization of the optic nerve head (enlarged cup-to-disc ratio) and visual field testing.
Treatment	Treatment to ↓ IOP uses a combination of topical and systemic therapy as follows: ▪ Eye drops (timolol, apraclonidine, pilocarpine, dorzolamide, latanoprost) ▪ Systemic medications (oral or IV acetazolamide, or IV mannitol) ▪ Laser peripheral iridotomy, which creates a hole in the peripheral iris, is curative, and can be performed prophylactically The patient should not have any medications that cause pupillary dilation (atropine or other medications with anticholinergic activity such as antihistamines and antidepressants).	Topical medications such as prostaglandins (latanoprost) and cholinergic agonists (pilocarpine) ↑ aqueous outflow, whereas β-blockers (timolol, betaxolol) and carbonic anhydrase inhibitors (acetazolamide) ↓ aqueous production. Alpha-agonists (apraclonidine, brimonidine) work via both mechanisms. Prostaglandins or β-blockers are chosen as first-line therapy. If medication fails, laser trabeculoplasty or a trabeculectomy can improve aqueous drainage.

CATARACT

- Lens opacification resulting in obstructed passage of light (Fig. 2.9-36). Associated with diabetes, HTN, advanced age, and exposure to radiation or corticosteroids. Congenital risk factors: classic galactosemia, galactokinase deficiency, trisomies (13, 18, 21), TORCH infections (eg, rubella), Marfan syndrome, Alport syndrome, myotonic dystrophy, and neurofibromatosis 2.

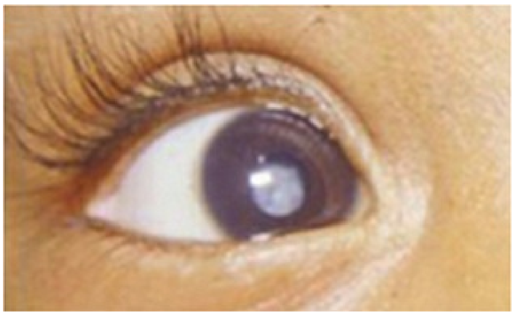


FIGURE 2.9-36. **Cataract.** (Reproduced with permission from Roshan M, Kabekkodu SP, Vijaya PH, et al. Analysis of mitochondrial DNA variations in Indian patients with congenital cataract. *Mol Vis.* 2012;18:181–193.)

- ***Hx/PE:*** Presents with reduced visual acuity, especially at night, and loss of the red reflex.

- ***Tx:*** Surgical lens removal and replacement.

Q

A 39-year-old man presents to the emergency department with severe eye pain, photophobia, and a persistent sensation that something is in his eye. The physician is suspicious of a corneal abrasion. What are the risk factors for this condition, and what diagnostic test can you do to confirm your suspicion?

AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD) is more common among White individuals, females, people who smoke, and those with a family history.

History/PE

- Presents with painless loss of central vision. Early signs include distortion of straight lines (metamorphopsia) and loss of other aspects of fine visual acuity.

A

Risk factors for corneal abrasion include trauma, foreign body, and contact lens use. Use a penlight to document pupillary function and the presence/absence of a foreign body. A fluorescein examination can be diagnostic and will show a corneal staining defect. Pain persists even after departure of foreign body due to damage and sensitization of corneal nerves.

- **Atrophic ("dry") macular degeneration:** Responsible for 80% of cases. It causes gradual vision loss.
- **Exudative or neovascular ("wet") macular degeneration:** Much less common but associated with more rapid and severe vision loss.

Diagnosis

- **Atrophic ("dry") macular degeneration:** Fundoscopy reveals drusen (accumulation of white/yellow extracellular material) and/or pigmentary changes (Fig. 2.9-37).

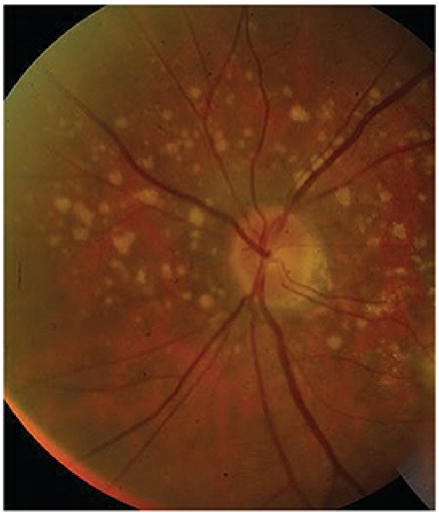


FIGURE 2.9-37. **Macular degeneration with evidence of drusen and fibrosis on fundoscopic exam.** (Reproduced with permission from USMLE-Rx.com.)

- **Exudative or neovascular (“wet”) macular degeneration:** Hemorrhage and subretinal fluid are present.

Treatment

- **Atrophic AMD:** No treatment is currently available, although a combination of vitamins (vitamin C, vitamin E, beta-carotene, and zinc) has been found to slow disease progression. The physician should be cautious about giving high doses of vitamin E and beta-carotene to patients who smoke, as there is an association of ↑ mortality rate from lung cancer in people taking high doses of these supplements.
- **Exudative AMD:** Intravitreal injections of VEGF inhibitors have been shown to improve vision (aflibercept, ranibizumab, bevacizumab) or slow visual loss in patients with exudative AMD.

RETINAL VASCULAR OCCLUSION

Occurs in older adult patients and is strongly related to cardiovascular disease (see Table 2.9-25).

TABLE 2.9-25. **Central Retinal Artery vs Central Retinal Vein Occlusion**

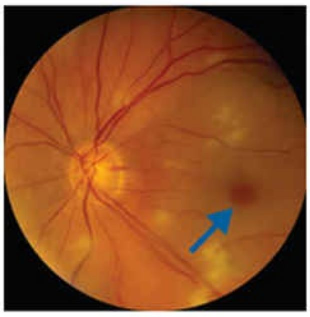
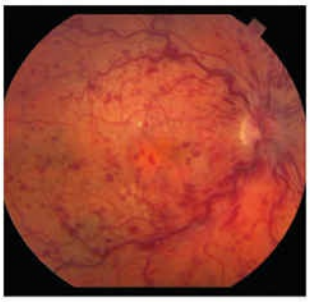
	CENTRAL RETINAL ARTERY OCCLUSION	CENTRAL RETINAL VEIN OCCLUSION
History/PE	Presents with sudden, painless, unilateral vision loss (eg, scotoma), as well as relative afferent pupillary defect Patients present with a cherry-red spot on the fovea (*blue arrow in image*), retinal swelling (whitish appearance to the nerve fiber layer), and retinal arteries that may appear bloodless Transient occlusion is comparable to transient ischemic attack and is known as amaurosis fugax 	Presents with rapid, painless vision loss of variable severity; associated with hypertension A swollen optic disc with hemorrhages, venous stasis retinal hemorrhages, cotton-wool spots, and macular edema may be seen on funduscopic exam 
Etiology	Atherosclerosis is the biggest risk factor; other risk factors include cardioembolism (atrial fibrillation, endocarditis), giant cell arteritis, Behcet syndrome, and sickle cell disease	Hypertension is the biggest risk factor; other risk factors include conditions that cause hypercoagulability (factor V Leiden, proteins C and S deficiency, antithrombin [AT] III deficiency, anti-phospholipid antibody syndrome, monoclonal gammopathies)
Workup	Diagnosis is based on history and fundoscopy The next best tests to order after diagnosis are a carotid duplex + echocardiogram to evaluate for atherosclerotic disease and cardioembolic sources Giant cell arteritis is ruled out using erythrocyte sedimentation rate and C-reactive protein in patients over 50 years who have no visualized retinal emboli	Hypercoagulability testing should be performed if there is a suggestive history or other causes have been excluded
Treatment	Ocular massage with high-flow oxygen administration; intra-arterial thrombolysis within 8 hours Other treatments target the specific etiology and may include anticoagulation, carotid endarterectomy, and secondary prevention of vascular events such as stroke or MI	Laser photocoagulation for ischemic central retinal vein occlusion (CRVO) to reduce risk of neovascularization VEGF inhibitors treat macular edema (cause of vision loss in CRVO); optimization of risk factor treatment ([HTN, diabetes mellitus [DM]) should occur

Image A reproduced with permission from USMLE-Rx.com. Image B reproduced with permission from Alasil T, Rauser ME. Intravitreal bevacizumab in the treatment of neovascular glaucoma secondary to central retinal vein occlusion: a case report. *Cases J.* 2009;2:176.

OPTIC NEURITIS

Inflammation of the optic nerve that is commonly associated with MS. Other optic neuropathies may be caused by ischemia, infection/postinfection (meningitis, encephalitis), vasculitis, connective tissue disease (systemic lupus erythematosus [SLE], Sjögren), genetic conditions, and drugs (eg, methanol, ethambutol, linezolid, infliximab).

KEY FACT

For optic neuritis, give IV, not oral, corticosteroids.

History/PE/Diagnosis

- Optic neuritis produces painful vision loss that is often unilateral. It causes relative afferent pupillary defect (Marcus-Gunn pupil).

- Fundoscopy may show disc swelling that looks similar to papilledema; however, fundoscopy is normal in two thirds of patients because the inflammation is posterior to the optic nerve head.
- The diagnosis is clinical, based on history and physical exam. Diagnosis may be confirmed with MRI of the orbits.

Treatment

Methylprednisolone IV for 3 days, followed by oral steroids. Oral steroids alone may increase risk of recurrence. Most patients gradually recover vision even without treatment, although IV methylprednisolone increases the rate of recovery.

RETINAL DETACHMENT

Separation of the retina from the underlying retinal pigment epithelium (RPE) and choroid. May be caused by retinal tears, proliferative diabetic retinopathy, or trauma. High myopia (>6 diopters of correction required) is a risk factor.

History/PE

- Sudden-onset painless monocular vision loss is often associated with floaters and flashes of light.
- Visual field defect may resemble a curtain ascending or descending over the eye.
- Retinal detachment and other trauma may cause vitreous hemorrhage, where the vitreous humor fills with blood. This complication presents with black spots and cobweb shapes in the visual field.

KEY FACT

Retinal detachment presents with sudden-onset flashing lights and blurred vision. Patients typically describe a curtain coming down over their eye. Ophthalmoscopy shows a gray, elevated retina.

Diagnosis

- All patients should have visual field and acuity testing.
- The detached retina can be seen floating in the posterior chamber on ultrasound.
- Definitive diagnosis requires a dilated funduscopic exam, where the detached retina can be directly visualized (Fig. 2.9-38).

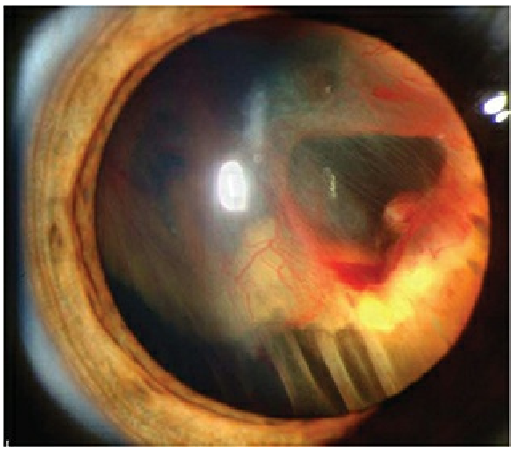


FIGURE 2.9-38. **Retinal detachment on fundoscopic examination.** (Reproduced with permission from USMLE-Rx.com.)

Treatment

Tamponading of the retina via surgery (vitrectomy or scleral buckle).

DIABETIC RETINOPATHY

Retinal damage due to chronic hyperglycemia. Two types:

- Nonproliferative—Damaged capillaries leak blood → lipids and fluid seep into retina causing hemorrhages and macular edema. Treatment: Blood sugar and blood pressure control.
- Proliferative—Chronic hypoxia results in new blood vessel formation with resultant traction on retina → retinal detachment. Treatment: Anti-VEGF injections, peripheral retinal photocoagulation, or surgery.

HYPERTENSIVE RETINOPATHY

- Chronic uncontrolled HTN → endothelial disruption → fibrinoid necrosis → retinal damage.
- Flame-shaped retinal hemorrhages, arteriovenous nicking, microaneurysms, macular star, cotton-wool spots (*blue arrow* in Fig. 2.9-43). Presence of papilledema in a hypertensive patient is indicative of malignant hypertension and requires immediate lowering of BP.
- Associated with risk of stroke, CAD, and kidney disease.

RETINITIS PIGMENTOSA

Inherited progressive dystrophy of RPE and photoreceptors. It may be associated with abetalipoproteinemia. Early findings include nyctalopia (night blindness) and peripheral vision loss. Fundoscopy may show triad of optic disc pallor, retinal vessel attenuation, and retinal pigmentation with bone spicule-shaped deposits (Fig. 2.9-39).

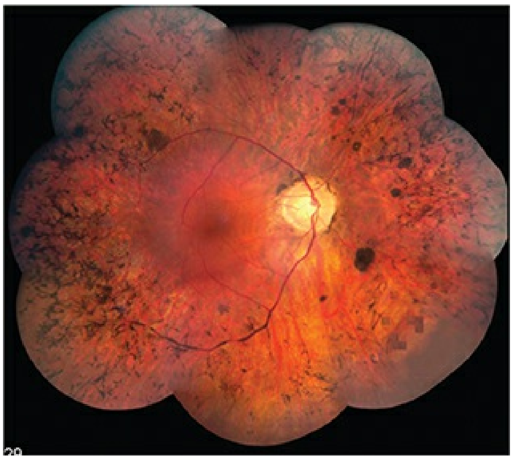


FIGURE 2.9-39. **Retinitis pigmentosa on fundoscopic exam.** (Modified with permission from USMLE-Rx.com.)

PAPILLEDEMA

Optic disc swelling with blurred disc margins and dilated/tortuous retinal veins (usually bilateral) due to ↑ ICP (eg, secondary to mass effect). Enlarged blind spot and elevated optic disc (Fig. 2.9-40) with blurred margins.

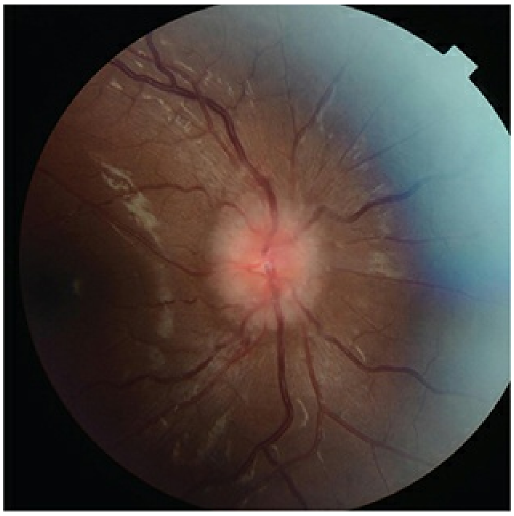


FIGURE 2.9-40. **Papilledema on fundoscopic exam.** (Modified with permission from USMLE-Rx.com.)

LEUKOCORIA

Loss (whitening) of the red reflex (Fig. 2.9-41). Important causes in children include retinoblastoma and congenital cataract.

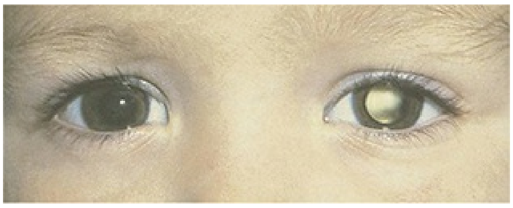


FIGURE 2.9-41. **Leukocoria with loss of red reflex.** (Reproduced with permission from Aerts I, Lumbroso-Le Rouic L, Gauthier-Villars M, et al. Retinoblastoma. *Orphanet J Rare Dis.* 2006;1:31. Published 2006 Aug 25. doi:10.1186/1750-1172-1-31.)

RELATIVE AFFERENT PUPILLARY DEFECT

Also called Marcus-Gunn pupil. When the light shines into a normal eye, constriction of the ipsilateral (direct reflex) and contralateral pupil (consensual reflex) is observed. When the light is then swung to the affected eye (side of optic nerve defect), both pupils dilate instead of constricting due to impaired conduction of a light signal along the injured optic nerve. It is associated with optic neuritis (eg, MS) and optic neuropathies (eg, giant cell arteritis).

HORNER SYNDROME

Sympathetic denervation of face causing:

- Ptosis (slight drooping of eyelid: superior tarsal muscle)
- Anhidrosis (absence of sweating) and flushing of affected side of face
- Miosis (pupil constriction)

Associated with lesions along the sympathetic chain (Fig. 2.9-42):

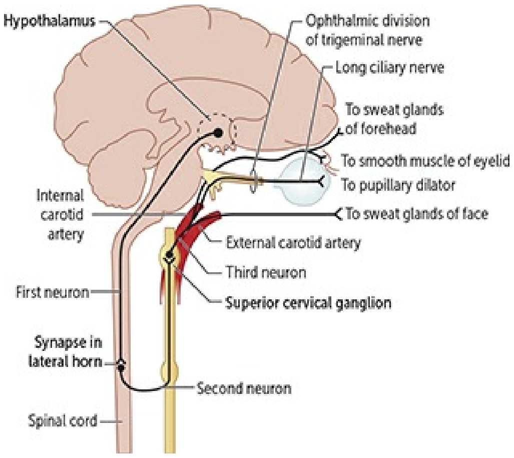

Hypothalamus
Ophthalmic division of trigeminal nerve
Long ciliary nerve
To sweat glands of forehead
To smooth muscle of eyelid
To pupillary dilator
To sweat glands of face
Internal carotid artery
External carotid artery
Third neuron
Superior cervical ganglion
First neuron
Synapse in lateral horn
Second neuron
Spinal cord

FIGURE 2.9-42. **Sympathetic chain anatomy in Horner syndrome.** (Reproduced with permission from USMLE-Rx.com.)

- First neuron: Pontine hemorrhage, lateral medullary syndrome, spinal cord lesion above T1 (eg, Brown-Séquard syndrome, late-stage syringomyelia)
- Second neuron: Stellate ganglion compression by Pancoast tumor
- Third neuron: Carotid dissection (painful); anhidrosis usually absent

ORBITAL BLOWOUT FRACTURE

Orbital floor fracture; usually caused by direct trauma to eyeball or intraorbital rim. ↑ risk of inferior rectus muscle and/or orbital fat entrapment. It may lead to infraorbital nerve injury.

CAVERNOUS SINUS SYNDROME

Cavernous sinus syndrome presents with variable ophthalmoplegia (CNs III and VI involved most frequently), ↓ corneal sensation, Horner syndrome, and decreased maxillary sensation. Secondary to pituitary tumor mass effect, carotid-cavernous fistula, or cavernous sinus thrombosis related to infection

INTRANUCLEAR OPHTHALMOPLEGIA

- MLF: Pair of tracts that interconnect CN VI and CN III nuclei (Fig. 2.9-43). Coordinates both eyes to move in same horizontal direction. When patient looks left, the left nucleus of CN VI fires, which contracts the left lateral rectus and stimulates the contralateral (right) nucleus of CN III via the right MLF to contract the right medial rectus. Lesions may be unilateral or bilateral (latter classically seen in MS, stroke).

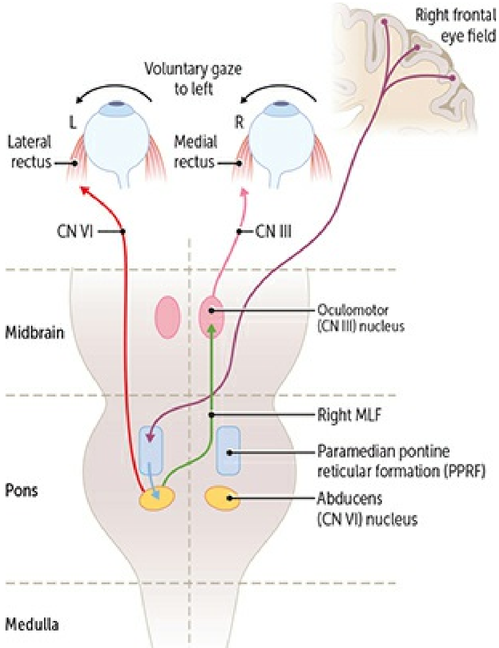

Right frontal eye field
Voluntary gaze to left
L
R
Lateral rectus
Medial rectus
CN VI
CN III
Midbrain
Oculomotor (CN III) nucleus
Right MLF
Paramedian pontine reticular formation (PPRF)
Pons
Abducens (CN VI) nucleus
Medulla

FIGURE 2.9-43. **Neural pathways associated with intranuclear ophthalmoplegia**. (Reproduced with permission from USMLE-Rx.com.)

medpx

- Lesion in MLF: Internuclear ophthalmoplegia (INO), a conjugate horizontal gaze palsy. Lack of communication occurs so that when CN VI nucleus activates ipsilateral lateral rectus, the contralateral CN III nucleus does not stimulate the medial rectus to contract. Abducting eye displays nystagmus (CN VI overfires to stimulate CN III). Convergence is normal.
- Directional term (eg, right INO, left INO) refers to the eye that is unable to adduct.

MNEMONIC

INO—

Ipsilateral adduction failure,
Nystagmus **O**pposite.

OTOLOGY

OTITIS MEDIA

Acute Otitis Media

History/PE

Pain in the ear, redness, decreased hearing, and fever. On otoscopy, bulging, hypomobile, and decreased light reflex of tympanic membrane are seen.

Diagnosis

Best initial test: Usually empirically treated with antibiotics. Consider tympanocentesis with culture in case of recurrent infections.

Treatment

Initial best treatment: Amoxicillin for 10 days. If no response, the patient has been treated with amoxicillin recently, or symptoms return within 1 month, amoxicillin-clavulanate should be used.

Chronic Suppurative Otitis Media

Similar to acute otitis media except:

- Continuous suppuration for >6 weeks with tympanic membrane perforation
- Prolonged duration of symptoms—drainage, pain, and hearing loss
- Absence of systemic symptoms such as fever

Otitis Media With Effusion/Serous Otitis Media/Glue Ear

Fluid in the middle ear for >3 months without an infection.

History/PE

- May be asymptomatic. Painless pressure in the ear post–acute otitis media in children.
- Otoscopy shows air-fluid level behind the bulging tympanic membrane and hypomobility.

Q

A 55-year-old man presents to the emergency department with sudden-onset headache and a dilated pupil in his right eye that is nonreactive to light. His right eye is hard to the touch. What is the most likely diagnosis, and what medications should be avoided in this patient?

Treatment

Monitoring for 3 months. If hearing impairment is resulting in speech impairment, tymapnostomy tubes may be considered.

OTITIS EXTERNA

Inflammation of the external auditory canal, also known as “swimmer’s ear.” *Pseudomonas* and *Staphylococcus* are the most common etiologic agents. Both grow in the presence of excess moisture. Necrotizing (malignant) otitis externa (*Pseudomonas* in >95%) can lead to osteomyelitis of the skull base.

History/PE

Presents with pain, pruritus, hearing loss, and possible purulent discharge. Examination reveals pain with movement of the tragus/pinna (unlike otitis media), an edematous and erythematous ear canal, and granulation tissue if necrotizing type. Cranial nerve palsies may be visible in the necrotizing type. See the Pediatrics chapter for a discussion of otitis media.

Diagnosis

A clinical diagnosis. A culture for severe or refractory cases. CT scan if the patient appears toxic.

Treatment

- **Best initial treatment**: Aural toilet (clean and dry ear [eg, using wick and/or astringents]).
- Mild otitis externa can be treated with topical acetic acid (7–10) days.
- Moderate otitis externa is treated with topical antibiotics (ofloxacin or ciprofloxacin) and steroid ear drops.
- Older adults with diabetes and individuals who are immunocompromised are at risk for necrotizing otitis externa and may require IV antibiotics (usually a fluoroquinolone or fourth-generation cephalosporin).
- Consider wick placement if occlusion of canal.
- To prevent, patients should avoid getting moisture in the ear and should thoroughly dry their ears after swimming,

MALIGNANT OTITIS EXTERNA

History/PE

- Severe infection of the external auditory meatus occurs with ear pain and suppurative drainage. Granulation tissue is seen on otoscopy. Malignant otitis externa is commonly seen in patients with poorly controlled diabetes and individuals who are immunosuppressed.
- Complications include cranial osteomyelitis and facial nerve palsy.
- The cause is *Pseudomonas* infection.

Treatment

- Drug of choice—IV ciprofloxacin. Other IV antibiotics against *Pseudomonas* can also be used (eg, ceftazidime, cefepime, quinolones, aztreonam, piperacillin/tazobactam).
- Surgical debridement and biopsy are required with failure to respond to antibiotics.

A

This patient’s presentation is consistent with closed-angle glaucoma. The physician should avoid pupil-dilating medications such as atropine, which will ↑ IOP and prevent drainage of aqueous humor.

SENSORINEURAL HEARING LOSS

Etiology

- Ménière disease—hearing loss, tinnitus, vertigo, and aural fullness due to excessive endolymph in the inner ear.
- Presbycusis—bilateral, symmetric age-related hearing loss to high-frequency sounds due to degenerative changes in inner ear and CN VIII. Hearing is worse in noisy environments.
- Drug-induced hearing loss

- Noise-induced hearing loss
- Acoustic neuroma

Diagnosis

See Figure 2.9-44.

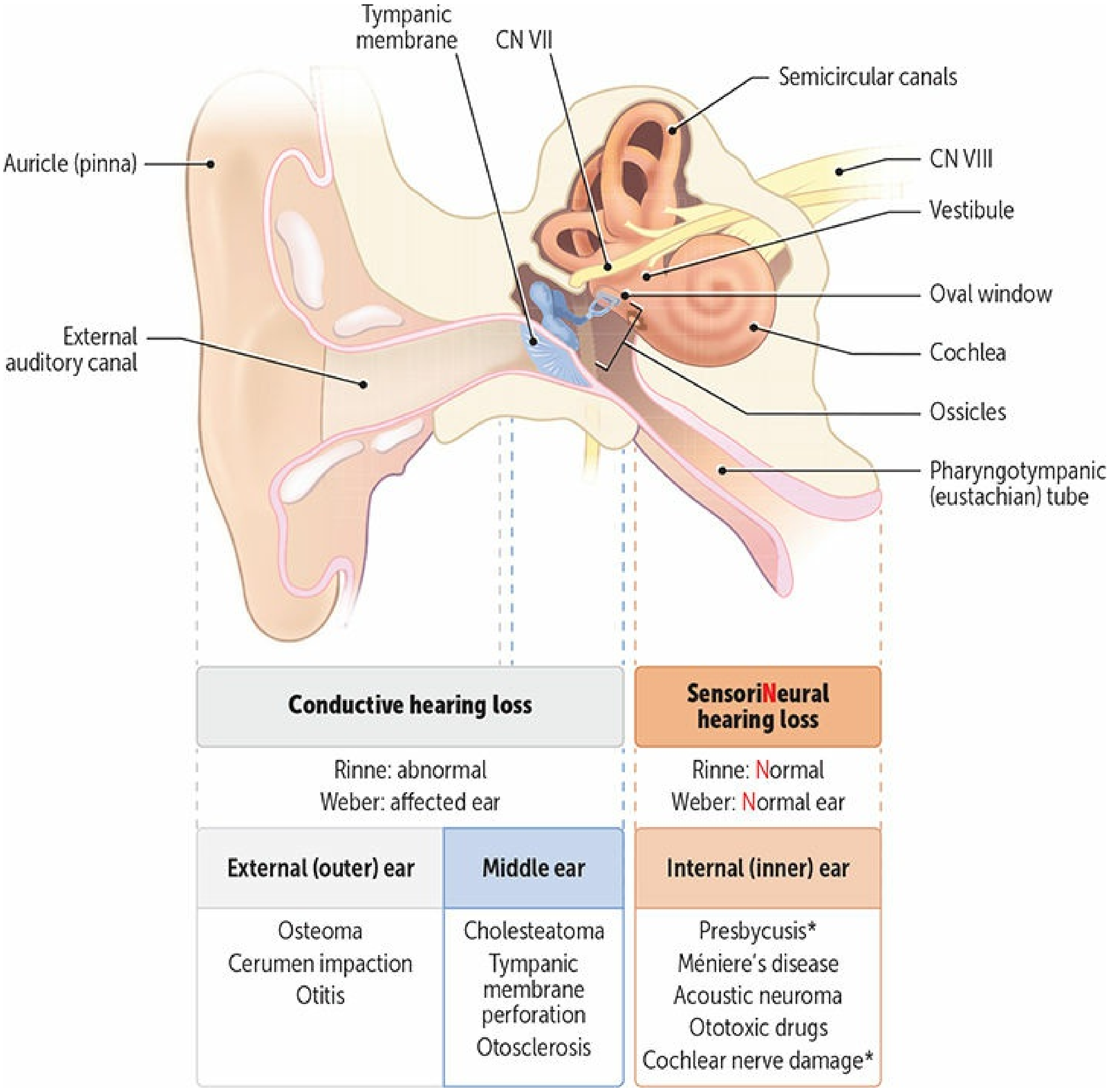

Tympanic membrane
CN VII
Semicircular canals
Auricle (pinna)
CN VIII
Vestibule
Oval window
External auditory canal
Cochlea
Ossicles
Pharyngotympanic (eustachian) tube
Conductive hearing loss
SensoriNeural hearing loss
Rinne: abnormal
Weber: affected ear
Rinne: Normal
Weber: Normal ear
External (outer) ear
Middle ear
Internal (inner) ear
Osteoma
Cerumen impaction
Otitis
Cholesteatoma
Tympanic membrane perforation
Otosclerosis
Presbycusis*
Méniere's disease
Acoustic neuroma
Ototoxic drugs
Cochlear nerve damage*

FIGURE 2.9-44. **Diagnosing hearing loss.** (Reproduced with permission from USMLE-Rx.com.)

- Rinne test: Reduced bilaterally
- Weber test: Localized to normal ear
- Pure tone audiometry: Increased auditory threshold in air and bone conduction
- Other tests include impendence audiometry and otoscopy for visual assessment

CONDUCTIVE HEARING LOSS

Etiology

- Otitis media: Acute, chronic suppurative, serous
- Wax impaction

- Cholesteatoma: Growth of keratinizing squamous epithelium, which erodes ear ossicles; on otoscopy, discrete white plaque is seen on the tympanic membrane
- Otosclerosis: Sclerotic changes in the ear ossicles

Diagnosis

See Figure 2.9-44.

- Rinne test: Bone > air
- Weber test: Localized to affected ear
- Pure tone audiometry: Increased auditory threshold in air conduction only

HIGH-YIELD FACTS IN

OBSTETRICS

The Basics of Pregnancy

Diagnosis of Pregnancy
- BETA-HUMAN CHORIONIC GONADOTROPIN (β-HCG)
- ULTRASONOGRAPHY

Physiologic Changes in Pregnancy

Prenatal Care and Diagnostic Testing
- GROUP B STREPTOCOCCUS TESTING AND TREATMENT
- PRENATAL DIAGNOSTIC TESTING

Teratology

Congenital Infections

Abortion
- SPONTANEOUS ABORTION
- ELECTIVE TERMINATION OF PREGNANCY
- COMPLICATIONS OF ABORTION

Maternal Complications of Pregnancy
- HYPEREMESIS GRAVIDARUM
- DIABETES
- HYPERTENSIVE DISEASE OF PREGNANCY
- URINARY TRACT INFECTIONS AND ASYMPTOMATIC BACTERIURIA
- INTRAHEPATIC CHOLESTASIS
- ACUTE FATTY LIVER IN PREGNANCY

Obstetric Complications of Pregnancy
- ECTOPIC PREGNANCY
- GESTATIONAL TROPHOBLASTIC DISEASE
- ANTEPARTUM HEMORRHAGE AND ABNORMAL PLACENTATION
- MULTIPLE GESTATION
- FETAL GROWTH RESTRICTION
- FETAL MACROSOMIA
- POLYHYDRAMNIOS
- OLIGOHYDRAMNIOS
- RH ISOIMMUNIZATION
- ANTEPARTUM FETAL SURVEILLANCE

Normal Labor and Delivery
- DEFINITION AND STAGES OF LABOR
- OBSTETRIC EXAMINATION
- FETAL HEART RATE MONITORING

OBSTETRIC ANALGESIA AND ANESTHESIA

Abnormal Labor and Delivery

INDICATIONS FOR C-SECTION
PRETERM LABOR
RUPTURE OF MEMBRANES
FAILURE TO PROGRESS
INTRA-AMNIOTIC INFECTION
FETAL MALPRESENTATION
UMBILICAL CORD PROLAPSE
SHOULDER DYSTOCIA
EPISIOTOMY
UTERINE INVERSION
UTERINE RUPTURE

Puerperium

POSTPARTUM HEMORRHAGE
POSTPARTUM INFECTION
PERIPARTUM CARDIOMYOPATHY
SHEEHAN SYNDROME (POSTPARTUM PITUITARY NECROSIS)

Lactation and Breastfeeding

PHYSIOLOGY
CONTRAINDICATIONS TO BREASTFEEDING
MASTITIS/BREAST ABSCESS
BREAST ENGORGEMENT
NIPPLE INJURY
LOCALIZED PLUGGED DUCT
GALACTOCELE

THE BASICS OF PREGNANCY

The terms and concepts that follow are central to an understanding of the physiologic processes of pregnancy:

Gravidity: Number of times a woman has been pregnant

Parity: Number of pregnancies that led to a birth beyond 20 weeks' gestational age or an infant weighing >500 g (1 lb, 2 oz).

- In prenatal assessment, TPAL expresses the number of term deliveries (T), the number of preterm deliveries (P), the number of abortuses (A), and the number of living children (L).

Embryonic age: Number of weeks + days since fertilization; usually unknown

Gestational age (GA): The number of weeks and days measured from the first day of the last menstrual period (LMP). GA can also be determined by the following:

- **Fundal height:** Reaches umbilicus (approximately 22 cm) at 20 weeks; +1 cm/week of gestational age thereafter
- **Fetal heart tones (Doppler):** Typically, 10 to 12 weeks
- **Quickening or appreciation of fetal movement:** Occurs at 16 weeks for multiparas and

20 weeks for primiparas at the earliest

- **Ultrasonography:**
  - **Most accurate dating method in early pregnancy:** Fetal crown-rump length (CRL) at 6 to 12 weeks
  - **Preferred measurement from 13 weeks+:** Biometry using biparietal diameter (BPD), femur length (FL), and abdominal circumference (AC)

KEY FACT

A G3P1 patient has had three pregnancies but only one birth beyond 20 weeks and/or an infant who weighs at least 500 g.

DIAGNOSIS OF PREGNANCY

β−HUMAN CHORIONIC GONADOTROPIN (β-hCG)

- The standard for diagnosing pregnancy. Can be detected in serum or urine.
- Serum β-hCG more sensitive and preferred if menstrual period is <1 week late.
- Produced by the placenta; peaks at 100,000 mIU/mL by 10 weeks.
- ↓ throughout the second trimester; plateaus in the third trimester.
- β-hCG levels double approximately every 48 hours during early pregnancy; failure of hCG levels to double every 48 hours concerning for miscarriage or ectopic pregnancy.

KEY FACT

Get a quantitative serum β-hCG:

- To help diagnose ectopic pregnancy and follow the trend for resolution after treatment
- To help diagnose miscarriage
- To monitor after treatment of trophoblastic disease (rising levels concerning for choriocarcinoma)
- To screen for fetal aneuploidy

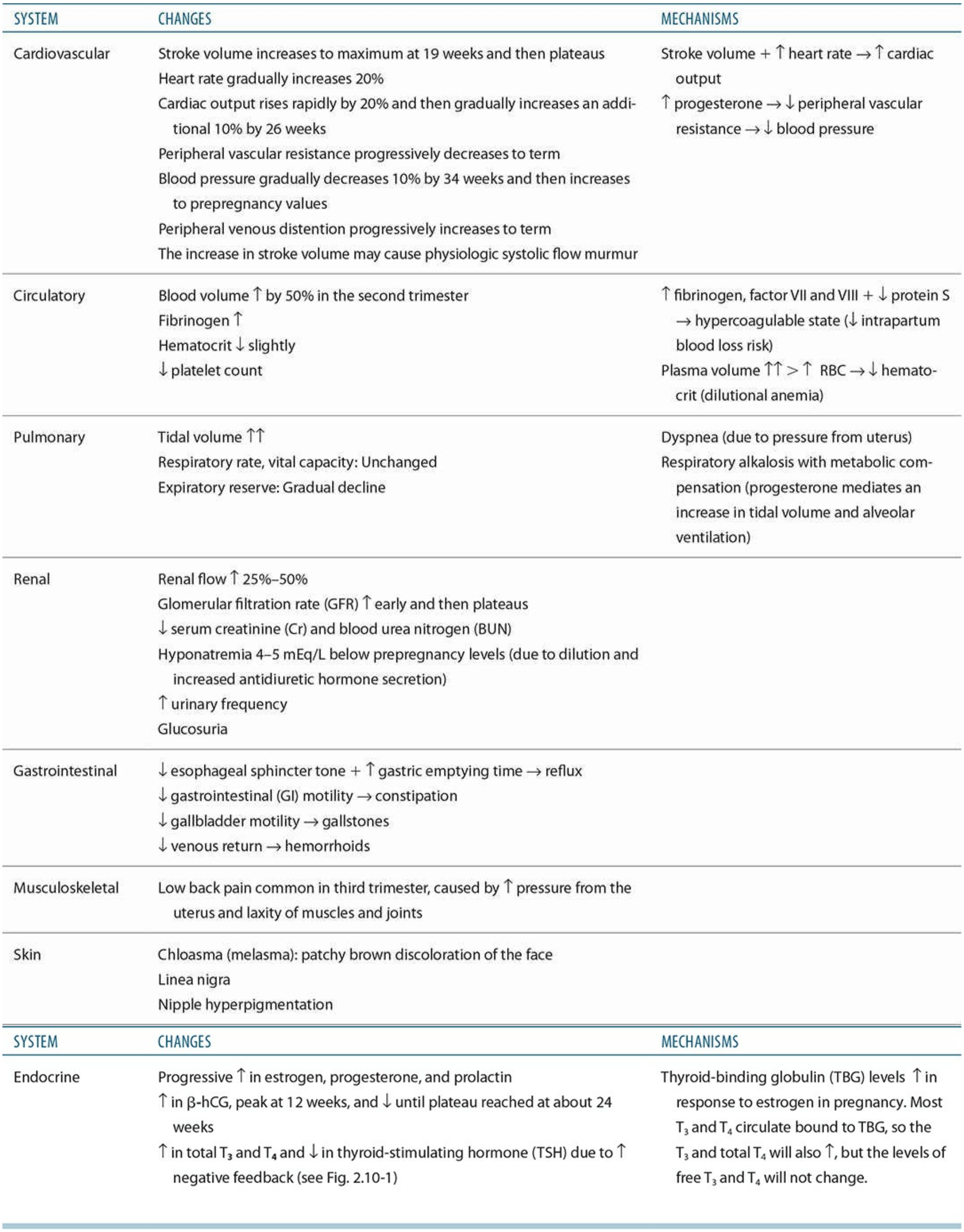
ULTRASONOGRAPHY

- Used to confirm an intrauterine pregnancy
- Gestational sac visible on transvaginal ultrasonography by:
  - 5 weeks
  - A β-hCG in the range of 1500 to 3500 mIU/mL
- Transabdominal ultrasound (US) typically reserved for second-/third-trimester measurements

PHYSIOLOGIC CHANGES IN PREGNANCY

Table 2.10-1 describes the physiologic changes seen in pregnancy, as well as their mechanisms. These changes occur to increase perfusion to the fetus, optimize materno-fetal gas exchange, and alter the maternal pelvis to aid in delivery.

TABLE 2.10-1. **Physiologic Changes in Pregnancy**



SYSTEM	CHANGES	MECHANISMS
Cardiovascular	Stroke volume increases to maximum at 19 weeks and then plateaus Heart rate gradually increases 20% Cardiac output rises rapidly by 20% and then gradually increases an additional 10% by 26 weeks Peripheral vascular resistance progressively decreases to term Blood pressure gradually decreases 10% by 34 weeks and then increases to prepregnancy values Peripheral venous distention progressively increases to term The increase in stroke volume may cause physiologic systolic flow murmur	Stroke volume + ↑ heart rate → ↑ cardiac output ↑ progesterone → ↓ peripheral vascular resistance → ↓ blood pressure
Circulatory	Blood volume ↑ by 50% in the second trimester Fibrinogen ↑ Hematocrit ↓ slightly ↓ platelet count	↑ fibrinogen, factor VII and VIII + ↓ protein S → hypercoagulable state (↓ intrapartum blood loss risk) Plasma volume ↑↑ > ↑ RBC → ↓ hematocrit (dilutional anemia)
Pulmonary	Tidal volume ↑↑ Respiratory rate, vital capacity: Unchanged Expiratory reserve: Gradual decline	Dyspnea (due to pressure from uterus) Respiratory alkalosis with metabolic compensation (progesterone mediates an increase in tidal volume and alveolar ventilation)
Renal	Renal flow ↑ 25%–50% Glomerular filtration rate (GFR) ↑ early and then plateaus ↓ serum creatinine (Cr) and blood urea nitrogen (BUN) Hyponatremia 4–5 mEq/L below prepregnancy levels (due to dilution and increased antidiuretic hormone secretion) ↑ urinary frequency Glucosuria	
Gastrointestinal	↓ esophageal sphincter tone + ↑ gastric emptying time → reflux ↓ gastrointestinal (GI) motility → constipation ↓ gallbladder motility → gallstones ↓ venous return → hemorrhoids	
Musculoskeletal	Low back pain common in third trimester, caused by ↑ pressure from the uterus and laxity of muscles and joints	
Skin	Chloasma (melasma): patchy brown discoloration of the face Linea nigra Nipple hyperpigmentation	
Endocrine	Progressive ↑ in estrogen, progesterone, and prolactin ↑ in β-hCG, peak at 12 weeks, and ↓ until plateau reached at about 24 weeks ↑ in total T_3 and T_4 and ↓ in thyroid-stimulating hormone (TSH) due to ↑ negative feedback (see Fig. 2.10-1)	Thyroid-binding globulin (TBG) levels ↑ in response to estrogen in pregnancy. Most T_3 and T_4 circulate bound to TBG, so the T_3 and total T_4 will also ↑, but the levels of free T_3 and T_4 will not change.

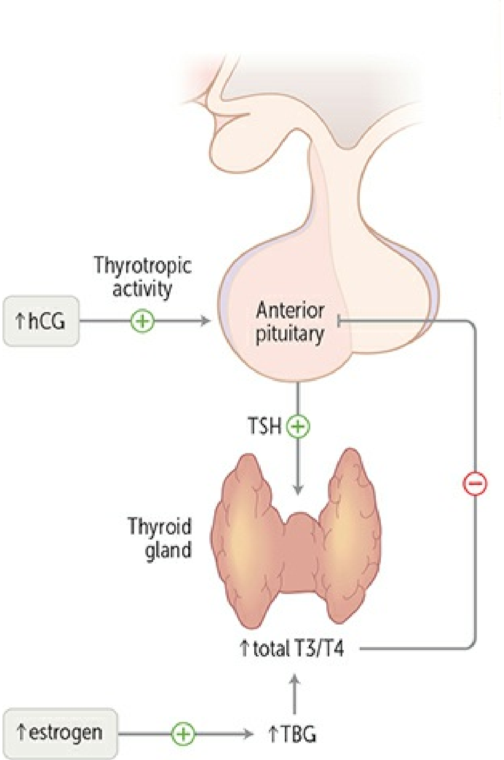

Thyrotropic activity
↑hCG
Anterior pituitary
TSH
Thyroid gland
↑total T3/T4
↑estrogen
↑TBG

FIGURE 2.10-1. **Effect of pregnancy on the pituitary-thyroid axis.** *hCG*, Human chorionic gonadotropin; *TBG*, thyroid-binding globulin; *TSH*, thyroid-stimulating hormone. (Reproduced with permission from USMLE-Rx.com.)

PRENATAL CARE AND DIAGNOSTIC TESTING

The goal of prenatal care is to prevent, diagnose, and treat conditions that can lead to adverse fetal or maternal outcomes in pregnancy. Expected weight gain, nutrition, and exercise recommendations are outlined in Table 2.10-2. Maternal failure to gain appropriate weight is associated with fetal growth restriction (FGR), whereas excess weight gain is associated with diabetes.

TABLE 2.10-2. **Recommendations for Standard Prenatal Care**

CATEGORY	RECOMMENDATIONS
Weight gain	Guidelines for weight gain according to prepregnancy body mass index (BMI): ▪ Underweight (BMI <18.5): 12–18 kg (28–40 lb) ▪ Acceptable (BMI 18.5–24.9): 11–16 kg (25–35 lb) ▪ Overweight (BMI 25–29.9): 7–11 kg (15–25 lb) ▪ Obese (all classes, BMI >30): 5–9 kg (11–20 lb)

Nutrition	Guidelines for nutritional supplementation:
	▪ An additional 100–300 kcal/day; additional 500 kcal/day during breastfeeding
	▪ Folic acid supplements 400 mcg daily or 4000 mcg if previous neural tube defect or maternal use of valproate or carbamazepine (folate supplementation ↓ neural tube defects for all reproductive-age women)
	▪ Iron
	▪ Calcium
	▪ Additional guidelines for vegans and others limiting meat/dairy intake:
	  ▪ Vitamin D
	  ▪ Vitamin B_{12}

Exercise	Thirty minutes of moderate exercise daily, while avoiding contact sports
Harmful substances	▪ Avoid fish with high mercury levels ▪ Moderate caffeine intake ▪ Avoid uncooked meat, fish, eggs ▪ Avoid unpasteurized dairy

GROUP B STREPTOCOCCUS TESTING AND TREATMENT

Screening for group B streptococcus (GBS): Rectovaginal swab at 36 to 38 weeks.

Indications for intrapartum prophylaxis:

- GBS-positive rectovaginal swab at 36 to 38 weeks
- GBS bacteriuria/urinary tract infection (UTI) any time during pregnancy
- Prior infant with early-onset GBS sepsis
- Unknown GBS status with any of the following: labor at <37 weeks, intrapartum fever, rupture of membranes >18 hours

Intrapartum prophylaxis: Intravenous (IV) penicillin (regardless of mode of birth); first-generation cephalosporins for patients with low-risk penicillin allergy; clindamycin or vancomycin for high risk of anaphylaxis

PRENATAL DIAGNOSTIC TESTING

Table 2.10-3 outlines a typical prenatal diagnostic testing schedule by week. The sections that follow describe each recommended screening modality.

TABLE 2.10-3. **Prenatal Visit and Diagnostic Testing Schedule**

	PRENATAL DIAGNOSTIC TESTING
Prenatal visits	Weeks 0–28: Every 4 weeks Weeks 29–35: Every 2 weeks Weeks 36–birth: Every week
Initial visit	Heme: Complete blood cell count (CBC); type and screen (important for determining Rh status) Infectious disease: Urinalysis (UA) and culture; rubella antibody titer; hepatitis B surface antigen (HBsAg); Hepatitis C antigen; rapid plasma reagin (RPR)/Venereal Disease Research Laboratory (VDRL); cervical gonorrhea and chlamydia; purified protein derivative (PPD); HIV; tuberculosis (TB) testing (or *Mycobacterium tuberculosis* [M.tb]); Pap smear (to check for dysplasia); consideration of hepatitis C vaccine (HCV) and varicella vaccine, based on history If indicated: Hemoglobin (Hb)A1c, sickle cell screening Discussion of genetic screening: Tay-Sachs disease, cystic fibrosis, spinal muscular atrophy
10–22 weeks	Aneuploidy screening: Multiple options are possible: ▪ Cell-free DNA screening most sensitive and specific screening tool available for trisomies 13, 18, and 21 (see Table 2.10-4). It is accepted as a primary screening option ▪ Full integrated test: Serum pregnancy-associated plasma protein A (PAPP-A) collected 11–14 weeks; crown-rump length measured 10–14 weeks, + quadruple screen in second trimester (hCG, inhibin A, alpha-fetoprotein, unconjugated estriol) ▪ Combined test: β-hCG, PAPP-A, measure of nuchal translucency 10–14 weeks
18–20 weeks	Ultrasonography for full anatomic screen
24–28 weeks	1-hour 50-gram glucose challenge test for gestational diabetes screen; if positive: 3-hour 100-gram glucose challenge test
28–30 weeks	Rh (D antigen[a]) immune globulin for Rh⊖ women (after antibody screen)
35–37 weeks	GBS culture; repeat CBC
34–40 weeks	In high-risk patients, cervical chlamydia and gonorrhea cultures, HIV, RPR

[a] Rh immune globulin to treat any unsensitized Rh⊖ woman during any occasion of fetal-maternal blood mixing (eg, spontaneous abortion [SAB], placental abruption, abdominal trauma) even if <28 weeks' gestation

Quadruple Screening

Quadruple screening consists of four elements (see Table 2.10-4): maternal serum α-fetoprotein (MSAFP), inhibin A, estriol, and β-hCG.

TABLE 2.10-4. **Quadruple Screening for Fetal Aneuploidy**

	MSAFP	ESTRIOL	INHIBIN A	β-HCG
Trisomy 18	↓	↓↓	↓↓	↓↓
Trisomy 21	↓	↓	↑	↑

- **MSAFP:** Produced by the fetus and enters the maternal circulation. Results are reported as multiples of the median (MoMs).
    - Measurement results depend on accurate gestational dating. Multiple gestations and uterine leiomyomata (fibroids) may cause size/date discrepancy.
    - MSAFP is rarely tested alone, as quad screening has ↑ sensitivity for detecting chromosomal abnormalities.
- ↑ **MSAFP (>2.5 MoMs)** is associated with the following:
    - Open neural tube defects (anencephaly, spina bifida)
    - Abdominal wall defects (gastroschisis, omphalocele)

  - Multiple gestation
  - Incorrect gestational dating
  - Fetal death
  - Placental abnormalities (eg, placental abruption)
- ↓ **MSAFP (<0.5 MoMs)** is associated with the following:
  - Trisomies 21 and 18
  - Incorrect gestational dating

KEY FACT

Still **UNDER** age at **18:** trisomy **18** = ↓ AFP, ↓ estriol, ↓↓ β-hCG, ↓ inhibin A

KEY FACT

2 up, 2 down: trisomy **21** = ↓ AFP, ↓ estriol, ↑ β-hCG, ↑ inhibin A

Nuchal Translucency

- Recommended at weeks 9 to 14
- PAPP-A + nuchal translucency + free β-hCG can detect ~91% of cases of Down syndrome and ~95% of cases of trisomy 18
- Advantages:
  - Available earlier than chorionic villus sampling (CVS) and less invasive than CVS (see following section on CVS)

Chorionic Villus Sampling

Table 2.10-5 outlines the relative advantages and disadvantages of CVS, cell-free fetal DNA, and amniocentesis (see Fig. 2.10-2).

TABLE 2.10-5. **Prenatal Screening for Fetal Genetic Abnormalities**

VARIABLE	CELL-FREE FETAL DNA	CHORIONIC VILLUS SAMPLING	AMNIOCENTESIS
GA	10 weeks	10–12 weeks	15–20 weeks
Procedure	Isolation of fetal DNA from blood sample obtained from pregnant patient	Transcervical or transabdominal aspiration of placental tissue	Transabdominal aspiration of amniotic fluid, using an ultrasound-guided needle
Advantages	Noninvasive	Genetically diagnostic Available at an earlier GA than amniocentesis	Genetically diagnostic
Disadvantages	May be limited because of low concentration of fetal DNA in maternal circulation	Risk for fetal loss relatively high (1%) Cannot detect open neural tube defects Limb defects associated with CVS at <9 weeks	Premature rupture of membranes (PROM), chorioamnionitis, fetal-maternal hemorrhage

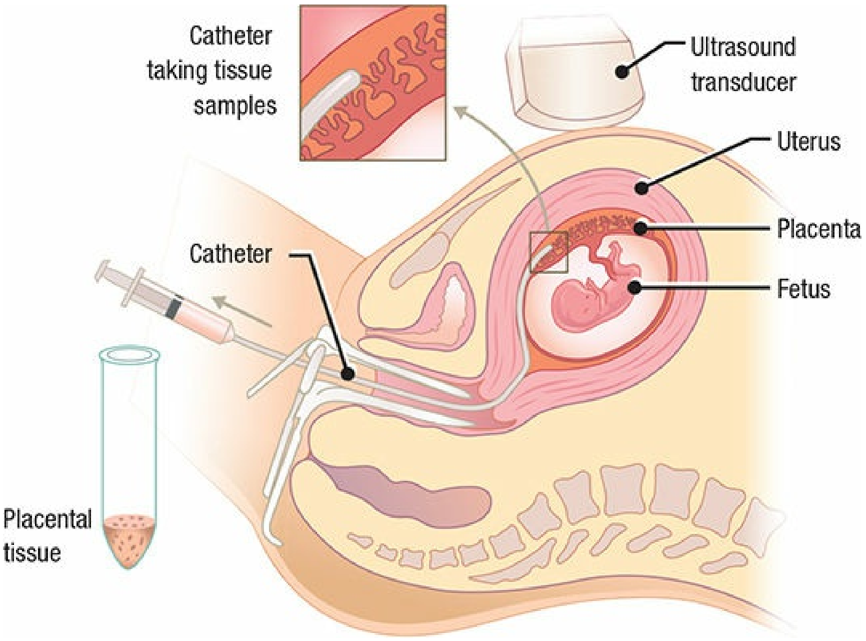

Catheter taking tissue samples
Ultrasound transducer
Uterus
Placenta
Fetus
Catheter
Placental tissue

FIGURE 2.10-2. **Chorionic villous sampling.** (Reproduced with permission from USMLE-Rx.com.)

Amniocentesis

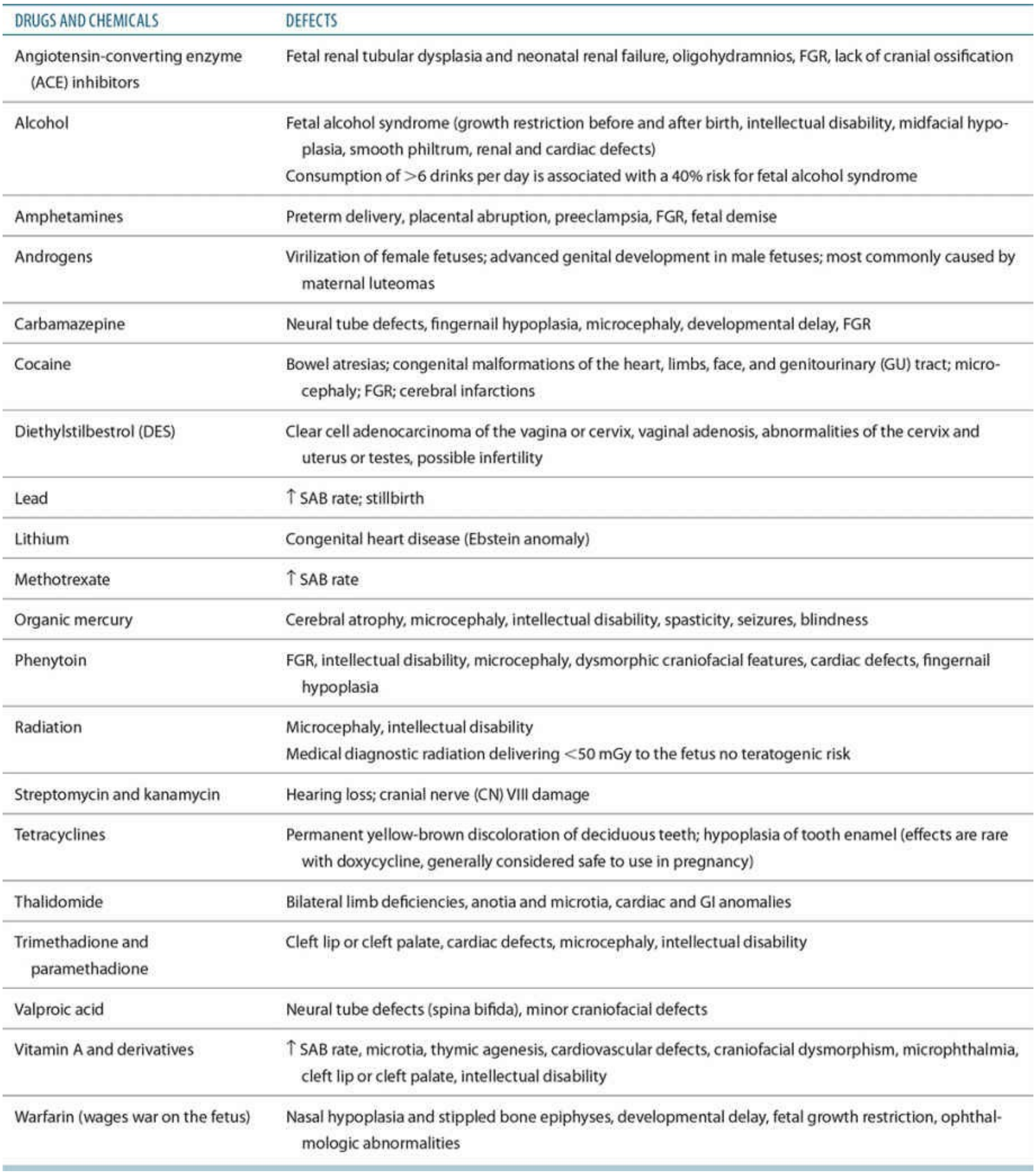
Indicated for the following:

- Concern for fetal genetic disease based on abnormal aneuploidy screening and/or ultrasound findings.
- Rh-sensitized pregnancy to obtain fetal blood type or to detect fetal hemolysis.
- Evaluation of fetal lung maturity. Lecithin-to-sphingomyelin ratio ≥2.5 or presence of phosphatidylglycerol (performed during the third trimester) indicates lung maturity.
- Assess for intraamniotic infection with Gram stain, culture.

TERATOLOGY

Major defects are apparent in about 3% of births and in roughly 4.5% of children by 5 years of age. Table 2.10-6 outlines common teratogenic agents.

TABLE 2.10-6. **Common Teratogenic Agents and Their Associated Defects**



DRUGS AND CHEMICALS	DEFECTS
Angiotensin-converting enzyme (ACE) inhibitors	Fetal renal tubular dysplasia and neonatal renal failure, oligohydramnios, FGR, lack of cranial ossification
Alcohol	Fetal alcohol syndrome (growth restriction before and after birth, intellectual disability, midfacial hypoplasia, smooth philtrum, renal and cardiac defects) Consumption of $>$6 drinks per day is associated with a 40% risk for fetal alcohol syndrome
Amphetamines	Preterm delivery, placental abruption, preeclampsia, FGR, fetal demise
Androgens	Virilization of female fetuses; advanced genital development in male fetuses; most commonly caused by maternal luteomas
Carbamazepine	Neural tube defects, fingernail hypoplasia, microcephaly, developmental delay, FGR
Cocaine	Bowel atresias; congenital malformations of the heart, limbs, face, and genitourinary (GU) tract; microcephaly; FGR; cerebral infarctions
Diethylstilbestrol (DES)	Clear cell adenocarcinoma of the vagina or cervix, vaginal adenosis, abnormalities of the cervix and uterus or testes, possible infertility
Lead	↑ SAB rate; stillbirth
Lithium	Congenital heart disease (Ebstein anomaly)
Methotrexate	↑ SAB rate
Organic mercury	Cerebral atrophy, microcephaly, intellectual disability, spasticity, seizures, blindness
Phenytoin	FGR, intellectual disability, microcephaly, dysmorphic craniofacial features, cardiac defects, fingernail hypoplasia
Radiation	Microcephaly, intellectual disability Medical diagnostic radiation delivering $<$50 mGy to the fetus no teratogenic risk
Streptomycin and kanamycin	Hearing loss; cranial nerve (CN) VIII damage
Tetracyclines	Permanent yellow-brown discoloration of deciduous teeth; hypoplasia of tooth enamel (effects are rare with doxycycline, generally considered safe to use in pregnancy)
Thalidomide	Bilateral limb deficiencies, anotia and microtia, cardiac and GI anomalies
Trimethadione and paramethadione	Cleft lip or cleft palate, cardiac defects, microcephaly, intellectual disability
Valproic acid	Neural tube defects (spina bifida), minor craniofacial defects
Vitamin A and derivatives	↑ SAB rate, microtia, thymic agenesis, cardiovascular defects, craniofacial dysmorphism, microphthalmia, cleft lip or cleft palate, intellectual disability
Warfarin (wages war on the fetus)	Nasal hypoplasia and stippled bone epiphyses, developmental delay, fetal growth restriction, ophthalmologic abnormalities

CONGENITAL INFECTIONS

Can occur at any time during pregnancy, labor, and delivery. Common sequelae include the following abnormalities:

- Premature delivery
- Central nervous system (CNS) abnormalities
- Anemia
- Jaundice
- Hepatosplenomegaly
- Growth restriction

MNEMONIC

ToRCHHeS

Toxoplasmosis
Rubella
Cytomegalovirus
HIV
Herpes viruses (herpes simplex virus, varicella zoster virus)
Syphilis

The most common pathogens involved in congenital infections can be remembered through use of the ToRCHHeS mnemonic (see Table 2.10-7).

TABLE 2.10-7. Diagnosis and Treatment of Common Congenital Infections

DISEASE	TRANSMISSION	SYMPTOMS	DIAGNOSIS	TREATMENT	PREVENTION
Toxoplasmosis	Transplacental; primary infection via consumption of raw meat or contact with cat feces	Hydrocephalus Intracranial calcifications Chorioretinitis	Serologic testing Ring-enhancing lesions on MRI	Pyrimethamine + sulfadiazine	Avoiding exposure to cat feces or uncooked meat during pregnancy
Rubella	Transplacental in the first trimester	Purpuric "blueberry muffin" rash Cataracts Intellectual disability Hearing loss Patent ductus arteriosus (PDA)	Serologic testing	Symptomatic	Immunization before pregnancy; vaccination of mother after delivery if serologic titers remain ⊖
CMV	Primarily transplacental	Petechial rash Periventricular calcifications	Urine culture; polymerase chain reaction (PCR) of amniotic fluid	Postpartum ganciclovir	N/A
HSV	Intrapartum transmission if the mother has active lesions; transplacental transmission rare	Skin, eye, and mouth infections Life-threatening CNS/systemic infection	Serologic testing	Acyclovir at 36 weeks until delivery	C-section if lesions are present at delivery
HIV	In utero, at delivery, or via breast milk	Often asymptomatic Failure to thrive Bacterial infections ↑ incidence of upper and lower respiratory diseases	Enzyme-linked immunosorbent assay (ELISA), Western blot	Highly active antiretroviral therapy (HAART)	Azidothymidine (AZT) or nevirapine in pregnant women with HIV; elective C-section if viral load is >1000 Treatment of infants with prophylactic AZT; avoidance of breastfeeding

DISEASE	TRANSMISSION	SYMPTOMS	DIAGNOSIS	TREATMENT	PREVENTION
Syphilis	Intrapartum; transplacental transmission possible	Maculopapular skin rash Lymphadenopathy Hepatomegaly "Snuffles": Mucopurulent rhinitis Osteitis Late congenital syphilis: Saber shins Saddle nose CNS involvement Hutchinson triad: Peg-shaped central incisors, deafness, interstitial keratitis	Dark-field microscopy, VDRL/RPR, fluorescent treponemal antibody absorption (FTA-ABS)	Penicillin (if allergic, should desensitize and give penicillin)	Penicillin in pregnant patients who test ⊕
Zika virus	Transplacental transmission	Microcephaly Craniofacial disproportion Neurologic and ocular abnormalities	Zika RNA detection	None	Avoidance of tropical mosquito-infested regions

KEY FACT

Pregnant patients should not change a cat's litterbox to prevent exposure to toxoplasma.

ABORTION

SPONTANEOUS ABORTION

The loss of gestation before 20 weeks' gestation. More than 80% of cases occur in the first trimester. Associations are as follows:

- **Maternal factors:**
  - **Inherited thrombophilia:** Factor V Leiden, prothrombin, antithrombin, protein C and S deficiencies, methylene tetrahydrofolate reductase deficiency (hyperhomocysteinemia)
  - **Immunologic issues:** Antiphospholipid antibodies; alloimmune factors
  - **Anatomic issues:** Uterine and cervical abnormalities, cervical insufficiency, cervical conization or loop electrosurgical excision procedure (LEEP), cervical injury, diethylstilbestrol (DES) exposure
  - **Endocrinologic issues:** Diabetes mellitus (DM), hypothyroidism, progesterone deficiency
  - **Genetics:** Osteogenesis imperfecta type II; this is severe and lethal; infants present with multiple fractures and die in utero or shortly after birth.
  - **Other:** Maternal trauma, ↑ maternal age, infection, dietary deficiencies
- **Environmental factors:** Tobacco, alcohol, excessive caffeine (>500 mg/day), toxins, drugs, radiation
- **Fetal factors:**
  - Anatomic malformation
  - **Chromosomal abnormalities:** A factor in approximately 50% of spontaneous

abortions (SABs) in the first trimester, 20% to 30% in second-trimester losses, and 5% to 10% in third-trimester losses

- **Recurrent SAB:** Two or more consecutive SABs or three SABs in 1 year; causes dependent on timing; determining possible causes requires karyotyping of both parents, workup of mother for hypercoagulability, and evaluation of uterine anatomy
  - **Early (<12 weeks):** Chromosomal abnormalities likely cause
  - **Late (12–20 weeks):** Hypercoagulable states (eg, antiphospholipid syndrome, systemic lupus erythematosus [SLE], factor V Leiden, protein S deficiency), cervical insufficiency

If antiphospholipid antibodies are detected, false ⊕ Venereal Disease Research Laboratory (VDRL) and falsely prolonged partial thromboplastin time (PTT) may be seen. Low-molecular-weight heparin and low-dose aspirin provide prophylaxis against recurrent SAB.

History/PE

SAB can be categorized by visual examination of the cervical os (open vs closed) and the presence or status of the fetus and products of conception. See Table 2.10-8 for types of SAB.

TABLE 2.10-8. Types of Spontaneous Abortion

TYPE	SYMPTOMS/SIGNS	DIAGNOSIS	TREATMENT
Complete	Cessation of bleeding and cramping Expulsion of products of conception (POC)	Closed os Ultrasonography showing no POC	None
Threatened	Uterine bleeding ± abdominal pain (often painless) No POC expulsion	Closed os + intact membranes + fetal cardiac motion on ultrasonography	Follow-up ultrasonography to assess viability of fetus
Incomplete	Partial POC expulsion; bleeding/mild cramping	Visible tissue on examination Open os POC present on ultrasonography Treatment	Manual uterine aspiration (MUA) if <12 weeks or dilation and curettage (D&C); may also use misoprostol or expectant management in inevitable and missed SAB
Visible tissue on examination	Open os	POC present on ultrasonography	
Inevitable	Uterine bleeding and cramps No POC expulsion	Open os ± rupture of membranes (ROM) POC present on ultrasonography	
Missed	Asymptomatic ± cramping No bleeding	Closed os No fetal cardiac activity; POC present on ultrasonography	
Septic	Foul-smelling discharge, abdominal pain, fever, and cervical motion tenderness; ± POC expulsion Maternal mortality 10%–15%	Hypotension, hypothermia, ↑ WBC count Blood cultures	Manual uterine aspiration or D&C and IV antibiotics
Stillbirth	Absence of fetal cardiac activity >20 week	Uterus small for GA; no fetal heart tones or movement on ultrasonography	If <24 weeks, dilation and evacuation (D&E) If >24 weeks, induction of labor within 1–2 weeks, based on patient preference Offer autopsy to attempt to determine cause of death

Diagnosis

- Diagnosis by clinical presentation and physical examination
- **Nonviable pregnancy:** Gestational sac >25 mm without a fetal pole or absence of fetal cardiac activity when CRL >7 mm on transvaginal ultrasonography
- **Best initial test:** Ultrasonography can identify the following:
  - Gestational sac 5 to 6 weeks from the LMP
  - Fetal pole at 6 weeks
  - Fetal cardiac activity at 6 to 7 weeks
- **Next best test:** Serum β-hCG

Treatment

- See Table 2.10-8 for treatment specific to the type of SAB.
- Administer Rh immune globulin if the mother is Rh ⊖.

ELECTIVE TERMINATION OF PREGNANCY

It has been estimated that 50% of all pregnancies in the United States are unintended. About 25% of all pregnancies end in elective abortion. Options for elective abortion depend on GA and patient preference (see Table 2.10-9).

TABLE 2.10-9. Elective Abortion

TRIMESTER	PROCEDURE	GESTATIONAL AGE
First (90% of abortions)	Medical management: oral mifepristone (low dose) + oral/ vaginal misoprostol	<10 weeks
	Surgical management: - Manual uterine aspiration - Dilation and curettage (D&C) with vacuum aspiration	>10 weeks
Second (10% of abortions)	Obstetric management: induction of labor (typically with prostaglandins, amniotomy, and oxytocin)	13–24 weeks (depending on state laws)
	Surgical management: Dilation and evacuation (D&E)	Same as above

KEY FACT

If fever, vomiting, purulent discharge, and/or hemodynamic instability are seen after a spontaneous or elective abortion, **septic abortion** should be suspected. This is a medical emergency that requires broad-spectrum antibiotics and immediate surgery to remove infected tissue.

COMPLICATIONS OF ABORTION

- Septic abortion
- Retained products of conception → disseminated intravascular coagulation (DIC)
- Endometritis

MNEMONIC

The **I's** ***are*** **open.**

Findings in cervical exam during SAB: **I**nevitable and **I**ncomplete show **open** os.

MATERNAL COMPLICATIONS OF PREGNANCY

HYPEREMESIS GRAVIDARUM

Persistent vomiting not related to other causes, leading to starvation ketosis and weight loss (usually at least a 5% ↓ from prepregnancy weight).

- More common in first pregnancies, multiple gestations, and molar pregnancies
- ↑ β-hCG and ↑ estradiol have been implicated in pathophysiology

History/PE

Distinguished from nausea and vomiting of pregnancy (NVP) by severity (presence of weight loss and ketosis) and timing. Acid reflux, gastroenteritis, hyperthyroidism, and neurologic conditions can also cause NVP and should be on the differential diagnosis.

KEY FACT

Rule out trophoblastic disease with US in a pregnant patient who presents with severe nausea and vomiting.

Diagnosis

Clinical diagnosis.

- **Best initial test:** Ultrasonography; evaluation for trophoblastic disease or multiple gestation.
- Evaluation for electrolyte abnormalities (eg, hypokalemia), abnormal liver enzymes, amylase, and lipase.
- Wernicke encephalopathy from vitamin B_1 deficiency possible in severe cases. The physician can look for gait ataxia and oculomotor dysfunction.

Treatment

- **Best initial treatment:**
  - Dietary changes and doxylamine-pyridoxine
  - If no response, discontinue doxylamine-pyridoxine and use metoclopramide, promethazine, or prochlorperazine
  - Consider ondansetron if vomiting is not resolved with treatments mentioned earlier
- If dehydrated, administration of IV fluids, IV nutritional supplementation, and ondansetron IV

DIABETES

Diabetes in pregnancy is divided into the following two categories: pregestational DM and gestational DM.

- **Pregestational DM:** Onset before pregnancy (Type 1 or Type 2 DM)
- **Gestational DM:** Onset during pregnancy

Consider early screening (fasting glucose, first-trimester HbA1c, or early glucose tolerence test) for the following risk factors:

- Overweight or obese (BMI >25)
- Physical inactivity
- First-degree relative with DM
- Have previously given birth to an infant weighing 4000 g (approximately 9 lb) or more
- Previous gestational DM
- Women with polycystic ovarian syndrome
- Hemoglobin A1c (HbA1c) ≥5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing
- History of cardiovascular disease
- Other clinical conditions associated with insulin resistance (eg, metabolic syndrome, acanthosis nigricans)

Pregestational Diabetes

Observed in 1% of all pregnancies. Insulin requirements may ↑ as much as threefold. Poorly controlled DM is associated with an ↑ risk for congenital malformations, fetal loss, and maternal/fetal morbidity during labor and delivery.

KEY FACT

Greater than 8, investigate! If HbA1c is >8%, look for congenital abnormalities.

Testing and Treatment

Mother:

- Renal, ophthalmologic, and cardiac evaluation to assess for end-organ damage.
- **Best initial treatment:** Lifestyle modification with diet and exercise. Addition of insulin therapy if poor response.
- Strict glucose control is important to minimize fetal defects:
  - Fasting morning: ≤95 mg/dL
  - 2-hour postprandial: <120 mg/dL
- **Delivery and postpartum:**
  - Maintain normoglycemia (80–100 mg/dL) during labor with an IV insulin drip and hourly glucose measurements.
  - Consider delivery in the setting of poor maternal glucose control, preeclampsia, macrosomia, or evidence of fetal lung maturity (preferably after 32 weeks).
  - Consider C-section in the setting of an estimated fetal weight (EFW) >4500 g.

Fetus:

- **16–24 weeks:**
  - Ultrasonography to determine fetal anatomy (18–20 weeks)
- **32–34 weeks:**
  - Antepartum fetal surveillance (eg, nonstress test [NST], contraction stress test [CST], biophysical profile [BPP]) if poor glucose control or small vessel disease

  - Hospitalization if maternal DM has been poorly controlled or fetal parameters are a concern
  - Serial ultrasonograms for fetal growth

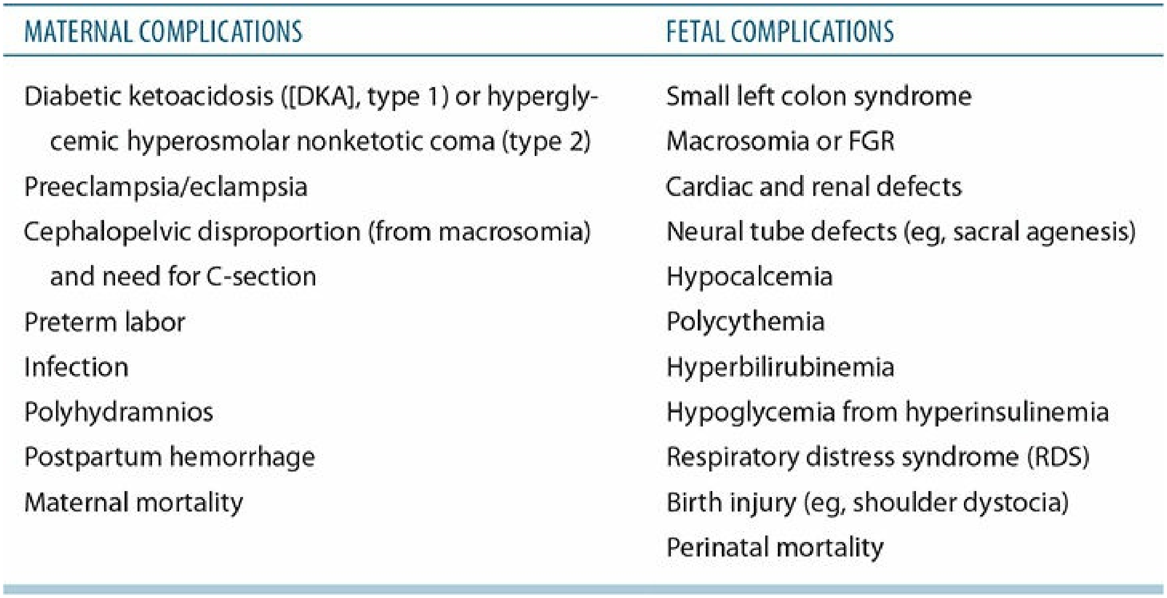
KEY FACT

Hyperglycemia in the first trimester suggests preexisting DM and should be managed as pregestational DM.

Complications

Pregestational DM is a risk factor for a variety of antepartum, intrapartum, and postpartum maternal and fetal complications (Table 2.10-10). Tight glycemic control is the best way to prevent these complications

TABLE 2.10-10. Complications of Pregestational Diabetes Mellitus



MATERNAL COMPLICATIONS	FETAL COMPLICATIONS
Diabetic ketoacidosis ([DKA], type 1) or hyperglycemic hyperosmolar nonketotic coma (type 2)	Small left colon syndrome
Preeclampsia/eclampsia	Macrosomia or FGR
Cephalopelvic disproportion (from macrosomia) and need for C-section	Cardiac and renal defects
Preterm labor	Neural tube defects (eg, sacral agenesis)
Infection	Hypocalcemia
Polyhydramnios	Polycythemia
Postpartum hemorrhage	Hyperbilirubinemia
Maternal mortality	Hypoglycemia from hyperinsulinemia
	Respiratory distress syndrome (RDS)
	Birth injury (eg, shoulder dystocia)
	Perinatal mortality

Gestational Diabetes

Carbohydrate intolerance of variable severity first diagnosed during pregnancy. Occurs in 3% to 5% of all pregnancies and is usually diagnosed in the second trimester (24–28 weeks).

History/PE

- Typically asymptomatic
- May present with edema, polyhydramnios, or a large-for-gestational-age infant (>90th percentile)

Diagnosis

- **Best initial test:** Routine screening with a 1-hour 50-g glucose challenge test
  - Venous plasma glucose measured 1 hour later
  - Performed at 24 to 28 weeks
  - Values ≥140 mg/dL considered abnormal
- Confirmation with an oral 3-hour (100-g) glucose tolerance test (GTT; next test if ⊕ screening test) showing any two of the following:

    - Fasting: >95 mg/dL
    - 1 hour: >180 mg/dL
    - 2 hours: >155 mg/dL
    - 3 hours: >140 mg/dL

Treatment

Mother:

- **Best initial treatment:** American Diabetes Association (ADA) diet, regular exercise, and strict glucose monitoring (four times per day).
- Insulin is the gold standard if dietary control is insufficient. Tight maternal glucose control (fasting ≤95 mg/dL; 1 hour postprandial ≤140 mg/dL; 2 hours postprandial ≤120 mg/dL) improves outcomes.
- Intrapartum insulin and dextrose to maintain tight control during delivery.

Fetus:

- Periodic ultrasonography and NSTs to assess fetal growth and well-being
- Recommended induction of labor at 39 to 40 weeks in patients with gestational diabetes controlled on insulin

KEY FACT

Keys to the management of gestational diabetes: (1) ADA diet, (2) insulin if needed, (3) ultrasonography for fetal growth, and (4) antepartum surveillance if requiring insulin or an oral hypoglycemic agent.

Complications

More than 50% of patients with gestational diabetes develop glucose intolerance and/or type 2 DM later in life. At 6 to 12 weeks postpartum, the physician should screen for DM (75-g 2-hour GTT) and repeat testing every 3 years if normal results.

HYPERTENSIVE DISEASE IN PREGNANCY

Chronic and Gestational Hypertension

Defined as follows:

- **Chronic hypertension:**
    - Presents before conception or at <20 weeks
    - Can be diagnosed postpartum if increased blood pressure (BP) persists for >12 weeks postpartum
    - Possibility for up to one third of patients with chronic hypertension to develop superimposed preeclampsia
- **Gestational hypertension:**
    - Idiopathic hypertension (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg measured twice >4 hours apart) without significant proteinuria (<300 mg/L)
    - Develops at ≥20 weeks
    - Possibility for up to 25% of patients with gestational hypertension to develop preeclampsia
    - Must normalize within 12 weeks after pregnancy

Treatment

- Close monitoring of BP
- **Best initial treatment:** Treatment with appropriate antihypertensives (eg, methyldopa, labetalol, nifedipine)
- If systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg, this is a hypertensive crisis that calls for labetalol, hydralazine, or nifedipine because of short onset of action
- The patient should not take angiotensin-converting enzyme (ACE) inhibitors or diuretics
    - ACE inhibitors are known to lead to uterine ischemia and fetal renal damage/defects
    - Diuretics can aggravate low plasma volume to the point of uterine ischemia

Complications

Similar to those of preeclampsia (see next).

Preeclampsia

- New-onset hypertension (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) and proteinuria (>300 mg of protein in a 24-hour period or elevated urine or protein/creatinine ratio of 0.3 or more) occurring at >20 weeks gestation up to 6 weeks postdelivery
- Preeclampsia with severe features defined as new-onset hypertension with new onset of any of the following features (with or without proteinuria):
    - Platelet count <100,000/μL
    - Serum creatinine >1.1 mg/dL or doubling of creatinine concentration in the absence of other renal disease
    - Liver transaminases at least twice the upper limit of normal
    - Pulmonary edema
    - Neurologic or visual symptoms
    - New-onset headache unresponsive to medication and not accounted for by alternative diagnoses
- **HELLP syndrome:** A variant of severe preeclampsia with severe features
- Consists of hemolytic anemia, elevated liver enzymes, and low platelets.
- Etiology unknown. Clinical manifestations are explained by vasospasm leading to distention of hepatic capsule, hemorrhage, and organ necrosis.
- Risk factors: Nulliparity, extremes of age (<20 or >35 years), multiple gestation, molar pregnancy, renal disease (caused by SLE or type 1 DM), a family history of preeclampsia, and chronic hypertension.

MNEMONIC

HELLP syndrome—

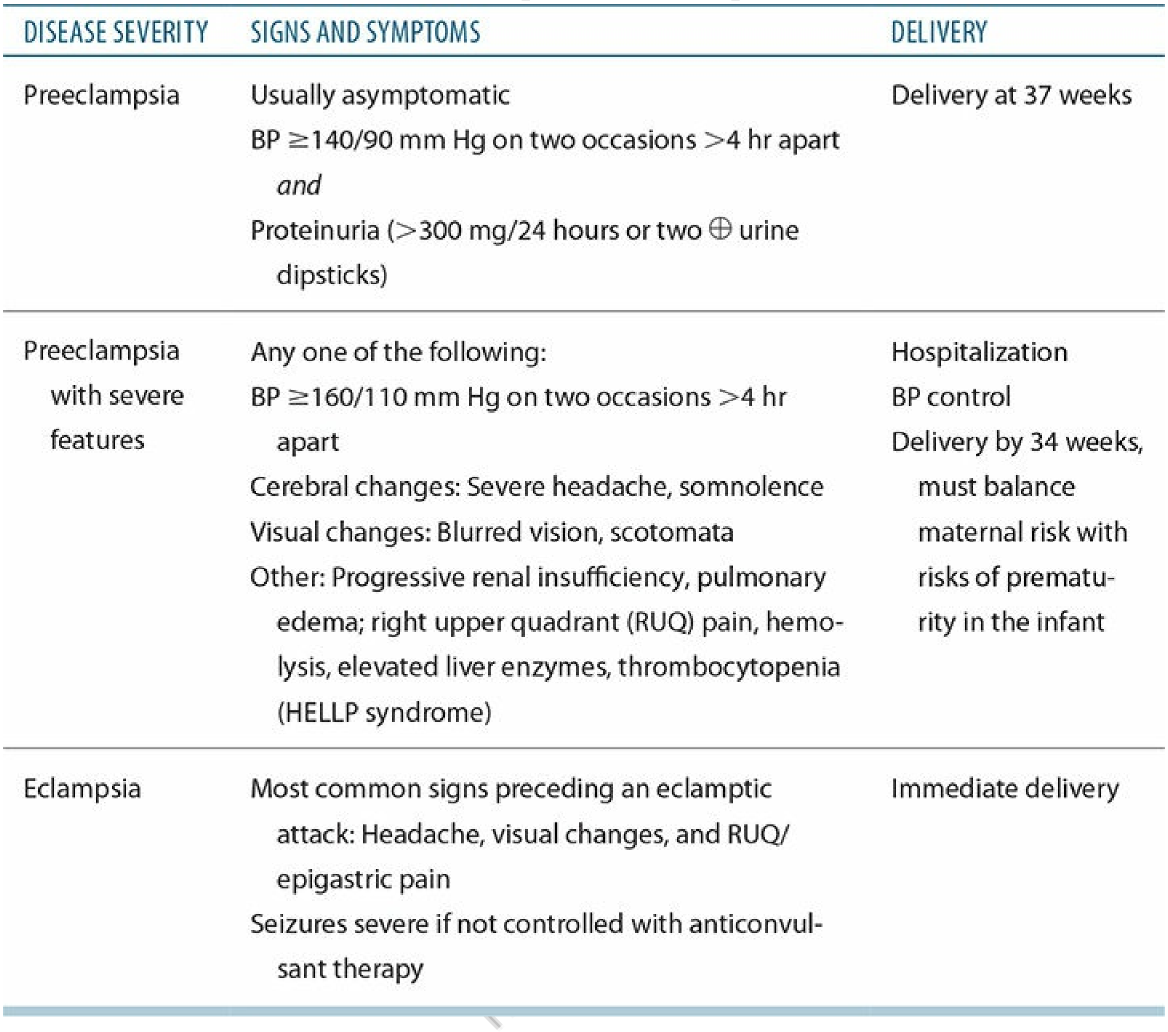
Hemolysis
Elevated liver function tests (**L**FTs)
Low **P**latelets

- Indication for delivery

History/PE

See Table 2.10-11 for the signs and symptoms of preeclampsia.

TABLE 2.10-11. **Presentation of Preeclampsia and Eclampsia**



DISEASE SEVERITY	SIGNS AND SYMPTOMS	DELIVERY
Preeclampsia	Usually asymptomatic BP ≥140/90 mm Hg on two occasions >4 hr apart *and* Proteinuria (>300 mg/24 hours or two ⊕ urine dipsticks)	Delivery at 37 weeks
Preeclampsia with severe features	Any one of the following: BP ≥160/110 mm Hg on two occasions >4 hr apart Cerebral changes: Severe headache, somnolence Visual changes: Blurred vision, scotomata Other: Progressive renal insufficiency, pulmonary edema; right upper quadrant (RUQ) pain, hemolysis, elevated liver enzymes, thrombocytopenia (HELLP syndrome)	Hospitalization BP control Delivery by 34 weeks, must balance maternal risk with risks of prematurity in the infant
Eclampsia	Most common signs preceding an eclamptic attack: Headache, visual changes, and RUQ/epigastric pain Seizures severe if not controlled with anticonvulsant therapy	Immediate delivery

Treatment

- Recommend low dose aspirin daily during pregnancy
- Delivery of the fetus is the only cure for preeclampsia.
- **Close-to-term or worsening preeclampsia:** Induce delivery with IV oxytocin, prostaglandin, or amniotomy.
  - Delivery should occur no later than 37 weeks.
- **Far from term (<34 weeks):** Provide expectant management with close surveillance; hospital admission for uncontrolled severe-range blood pressures.
- Prevent intrapartum seizures with a continuous magnesium sulfate drip.
  - Continue seizure prophylaxis for 24 hours postpartum.
  - Treat magnesium toxicity with IV calcium gluconate.
- **Preeclampsia with severe features:**
  - Control BP with labetalol and/or hydralazine (goal <160/110 mm Hg with a diastolic BP of 90–100 mm Hg to maintain fetal blood flow)
  - Provide a continuous magnesium sulfate drip
  - Deliver by induction or C-section once term

KEY FACT

Watch for signs of magnesium toxicity (loss of deep tendon reflexes [DTRs], respiratory paralysis, coma).

Complications

Prematurity, fetal distress, stillbirth, placental abruption, seizure, DIC, cerebral hemorrhage, serous retinal detachment, and fetal/maternal death.

Q

A 36-year-old G1P0 woman with a history of SLE at 36 weeks presents with headache and RUQ pain. She is admitted and found to have BPs of 165/100 and 170/105 mm Hg when tested twice 6 hours apart. She has 3+ protein on urine dipstick. Once her BP has been controlled with labetalol, what are the next steps in management?

Eclampsia

New-onset grand mal seizures in a patient with preeclampsia.

History/PE

See Table 2.10-11 for the signs and symptoms of eclampsia.

Treatment

- Delivery of the fetus is the only cure for eclampsia
- Management of maternal hypertension with labetalol or hydralazine
- Seizure control/prophylaxis with magnesium
  - If seizures recur, give IV diazepam
  - Monitor for clinical magnesium toxicity; there is no need to routinely monitor magnesium blood levels if renal function is normal
  - Monitor fetal status
  - Control BP
  - Limit fluids; use urinary Foley catheter for strict intake and output (I/Os)
- Initiate emergent delivery once the patient is stable and convulsions are controlled
- Postpartum management is the same as that for preeclampsia
- Seizures may occur antepartum (25%), intrapartum (50%), or postpartum (25%); most occur within 48 hours after delivery

Complications

Cerebral hemorrhage, aspiration pneumonia, hypoxic encephalopathy, thromboembolic events, and fetal/maternal death.

URINARY TRACT INFECTION AND ASYMPTOMATIC BACTERIURIA

Asymptomatic bacteriuria occurs in up to 7% of pregnant patients, and 30% to 40% will subsequently develop cystitis or pyelonephritis if untreated. Persistent untreated bacteriuria places the patient at a higher risk for preterm labor, low birth weight, and perinatal mortality. *Escherichia coli* is responsible for 70% to 90% of infections.

History/PE

- **Asymptomatic bacteriuria:** Screening 12 to 16 weeks, ⊕ urine culture on first-trimester screen ($\geq 10^5$ colony-forming units [CFUs])
- **Urinary tract infection (UTI):** Dysuria, urinary urgency, and frequency
- **Pyelonephritis:** Same as UTI + fever and costovertebral angle tenderness

Diagnosis

Best initial test: Urinalysis and ⊕ urine culture

Treatment

- **Asymptomatic bacteriuria and UTI:** 3 to 7 days nitrofurantoin (avoid in first trimester if possible), cephalexin, amoxicillin-clavulanate, or fosfomycin. No fluoroquinolones or TMP-SMX in first or third trimester. Do a follow-up culture at 1 week as test of cure.
- **Pyelonephritis:** Admittance to hospital, IV fluids, IV third-generation cephalosporins, suppressive antibiotics based on culture susceptibility for remainder of pregnancy, and follow-up culture for test of cure.
- GBS prophylaxis during time of delivery if GBS UTI at any time during pregnancy

A

The patient has preeclampsia with severe features. The next steps in management are to start a magnesium sulfate drip for seizure prophylaxis, give antihypertensive medications, and deliver by induction or C-section. The physician should check for end-organ involvement with labs (platelets, liver enzymes, and creatinine).

INTRAHEPATIC CHOLESTASIS

- **Symptoms:** Maternal pruritis, mainly on palms and soles. Can also present with right upper quadrant (RUQ) pain, sleep deprivation, and steatorrhea.
- **Labs:** Raised serum bile acids (most sensitive), increased aminotransferases, alkaline phosphatase, and total/direct bilirubin (less specific).
- **Risk:** Stillbirth, preterm delivery, and meconium-stained amniotic fluid.
- **Management:** Ursodeoxycholic acid and consideration of delivery at 36 weeks.

ACUTE FATTY LIVER IN PREGNANCY

Rare, life-threatening complication in the third trimester of pregnancy

- **Symptoms:** Nausea, vomiting, RUQ/epigastric pain, fulminant liver failure, scleral icterus
- **Labs:** Aminotransferases two times normal, increased bilirubin, thrombocytopenia, DIC, acute kidney injury, profound hypoglycemia
- **Management:** Immediate delivery due to high fetal and maternal mortality

OBSTETRIC COMPLICATIONS OF PREGNANCY

ECTOPIC PREGNANCY

Most often tubal (95%), but can be abdominal, ovarian, or cervical

History/PE

- Presents with unilateral lower abdominal pain and vaginal spotting/bleeding, although some patients are asymptomatic
- Associated with etiologies that cause damage to the fallopian tubes, including a history of pelvic inflammatory disease (PID), pelvic surgery, DES use, or endometriosis
- Differential diagnosis includes SAB, ovarian torsion, PID, and ruptured ovarian cyst

Diagnosis

- Evaluate for ectopic pregnancy in all females of reproductive age presenting with abdominal pain and positive pregnancy test
- **Best initial test:** Transvaginal ultrasonogram (see Fig. 2.10-3).

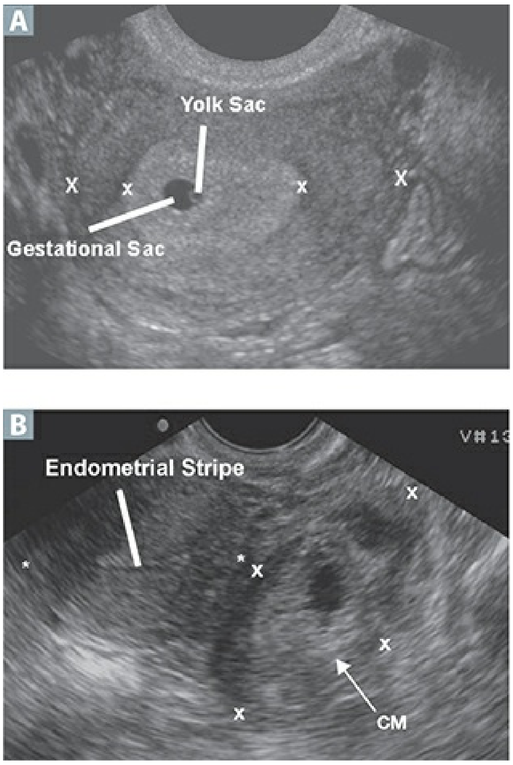


FIGURE 2.10-3. **Normal intrauterine pregnancy and ectopic pregnancy.** Transvaginal ultrasonograms showing **(A)** a normal intrauterine pregnancy with a gestational sac containing a yolk sac within the uterine cavity and **(B)** a complex mass *(CM)*/ectopic pregnancy adjacent to an empty uterus. (Reproduced with permission from Tintinalli JE et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 6th ed. New York, NY: McGraw-Hill; 2004.)

- **Next best test:** Serial serum β-hCG may be used to stratify hemodynamically stable patients in whom transvaginal US is nondiagnostic:
  - <3500 IU/L → serial β-hCG until levels reach 3500 IU/L (which is when an intrauterine pregnancy should be seen)
  - Levels in viable intrauterine pregnancy usually rise 50% to 100% in 48 hours
- >3500 IU/L → repeat β-hCG and US in 2 days

MNEMONIC

These symptoms* PAVE *the way for a diagnosis of ectopic pregnancy—

Pain (abdominal)
Amenorrhea OR
Vaginal bleeding
Ectopic pregnancy

Treatment

- Medical treatment (methotrexate) is sufficient for small, unruptured tubal pregnancies.
- Surgical options include salpingectomy or salpingostomy with evacuation (laparoscopy vs laparotomy).

KEY FACT

Unstable patients or those with signs of peritoneal irritation (eg, rebound tenderness) require emergent surgical intervention regardless of US findings and hCG levels.

Complications

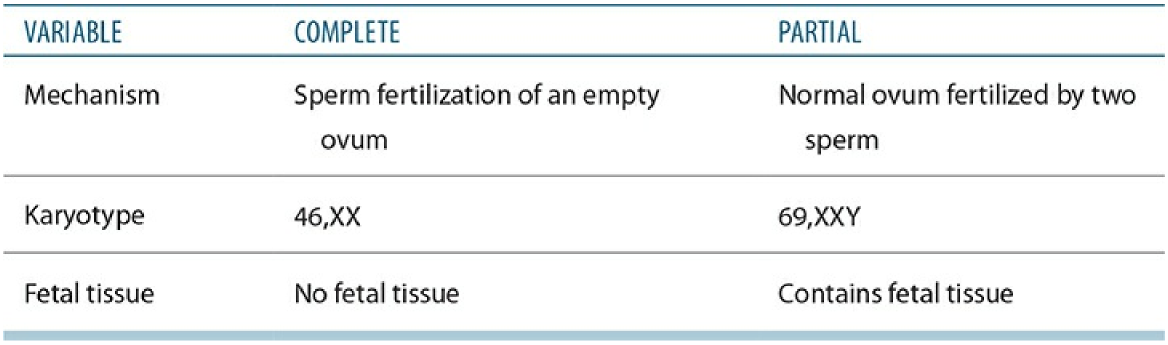
Tubal rupture and hemoperitoneum (a surgical emergency).

GESTATIONAL TROPHOBLASTIC DISEASE

A range of proliferative trophoblastic abnormalities that can be benign or malignant

- **Benign gestational trophoblastic disease (GTD):** It includes complete and partial molar pregnancies (see Table 2.10-12).

TABLE 2.10-12. Complete vs Partial Moles



VARIABLE	COMPLETE	PARTIAL
Mechanism	Sperm fertilization of an empty ovum	Normal ovum fertilized by two sperm
Karyotype	46,XX	69,XXY
Fetal tissue	No fetal tissue	Contains fetal tissue

- **Malignant GTD:** Molar pregnancy may progress to malignant GTD, including the following:
  - Invasive hydatidiform moles (10%–15%)
  - Choriocarcinoma (2%–5%)
- Complications of malignant GTD include pulmonary or CNS metastases and trophoblastic pulmonary emboli.

History/PE

- GTD presents with first-trimester uterine bleeding, hyperemesis gravidarum, preeclampsia/eclampsia at <24 weeks, and uterine size greater than dates.

- Risk factors include extremes of age (<20 or >40 years) and a diet deficient in folate or β-carotene.

Diagnosis

- **Initial test:** Pelvic examination may reveal enlarged ovaries (bilateral theca-lutein cysts) or expulsion of grapelike molar clusters into the vagina.
- **Next best/most accurate test:** Pelvic ultrasonography reveals a "snowstorm" appearance with no gestational sac or fetus present (see Fig. 2.10-4).

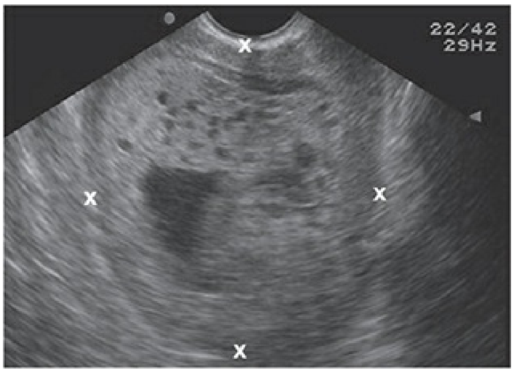


FIGURE 2.10-4. **Molar pregnancy.** Transvaginal ultrasonogram shows a large, complex intrauterine mass with cystic regions that have the characteristic appearance of grapes, also known as "snowstorm" appearance. (Reproduced with permission from Tintinalli JE et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide,* 6th ed. New York, NY: McGraw-Hill; 2004.)

- Labs show markedly ↑ serum β-hCG (usually >100,000 mIU/mL).
- X-ray of the chest (CXR) may show lung metastases.
- D&C reveals "cluster-of-grapes" tissue.

Treatment

- **Best initial treatment:** Evacuate the uterus with D&C.
- Follow with weekly β-hCG to undetectable (or negative) weekly, and then monthly for 6 months. Contraception for at least 6 months.
- Treat malignant disease with chemotherapy (methotrexate or dactinomycin).
- Treat residual uterine disease with hysterectomy.
- Chemotherapy and irradiation are highly effective for metastases.

ANTEPARTUM HEMORRHAGE AND ABNORMAL PLACENTATION

- Any bleeding that occurs after 20 weeks
- Complicates 3% to 5% of pregnancies
- **Most common causes:** Placental abruption and placenta previa (see Table 2.10-13 and Figs. 2.10-5 and 2.10-6)

TABLE 2.10-13. **Placental Abruption vs Placenta Previa vs Vasa Previa**

VARIABLE	PLACENTAL ABRUPTION	PLACENTA PREVIA	VASA PREVIA
Pathophysiology	Premature (before delivery) separation of normally implanted placenta	Abnormal placental location: Total: Placenta covers the cervical os Marginal: Placenta extends to the margin of the os Low lying: Placenta is in close proximity to the os	Velamentous umbilical cord insertion and/or bilobed placenta causing vessels to pass over the internal os
Incidence	1 in 100	1 in 200	1 in 2500
Risk factors	Hypertension, abdominal/pelvic trauma, tobacco or cocaine use, previous abruption, rapid decompression of an overdistended uterus, excessive stimulation	Prior C-sections, uterine surgeries, grand multiparity, advanced maternal age, multiple gestation, prior placenta previa	Multiple gestation, in vitro fertilization (IVF), accessory placental lobes, single umbilical artery, placenta previa, low-lying placenta
Symptoms	Painful vaginal bleeding that does not spontaneously cease Abdominal pain; uterine hypertonicity Fetal distress	Painless, bright red bleeding that often ceases in 1–2 hours with or without uterine contractions Usually no fetal distress	Painless bleeding at rupture of membranes with fetal bradycardia
Diagnosis	Primarily clinical Transabdominal/transvaginal ultrasonography sensitivity only 50%; the physician should look for a retroplacental clot; most useful for ruling out previa	Transabdominal/transvaginal ultrasonography sensitivity >95%; the physician should look for an abnormally positioned placenta. Partial previa can resolve as the lower uterine segment expands with pregnancy progression.	Transvaginal ultrasonography with color Doppler showing vessels passing over the internal os
Management	Stabilize patients with mild abruption and a premature fetus; manage expectantly (hospitalize; start IV and fetal monitoring; type and cross-match blood) Moderate to severe abruption: Immediate delivery is indicated (vaginal delivery with amniotomy if mother and fetus are stable and delivery is expected soon; C-section for maternal or fetal distress)	Do not perform a transvaginal exam or US Stabilize patients with a premature fetus; provide active surveillance Give tocolytics Use serial ultrasonograms to assess fetal growth, resolution of partial previa Administer betamethasone at 28–32 weeks to help with fetal lung maturity Deliver by C-section Indications for delivery include labor, life-threatening bleeding, fetal distress, documented fetal lung maturity, and 36 weeks	Acute bleeding = emergency C-section delivery Diagnosis before bleeding: Steroids at 28–32 weeks to help with fetal lung maturity, hospitalization at 30–32 weeks for close monitoring and scheduled C-section delivery as clinically indicated
Complications	Hemorrhagic shock DIC in 10% of patients Recurrence risk: 5%–15% Fetal hypoxia	Risk for placenta accreta Vasa previa Preterm delivery, PROM, FGR, congenital anomalies Recurrence risk: 4%–8%	Fetal exsanguination

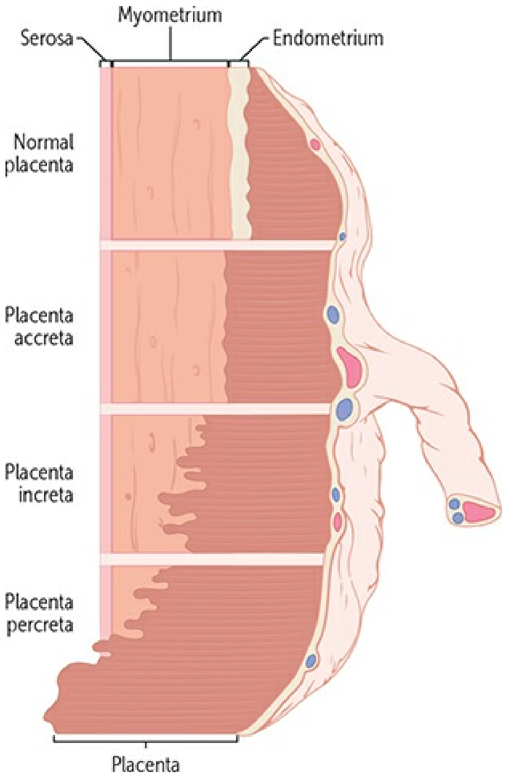

Myometrium
Serosa
Endometrium
Normal placenta
Placenta accreta
Placenta increta
Placenta percreta
Placenta

FIGURE 2.10-5. **Placenta accreta spectrum.** (Reproduced with permission from USMLE-Rx.com.)

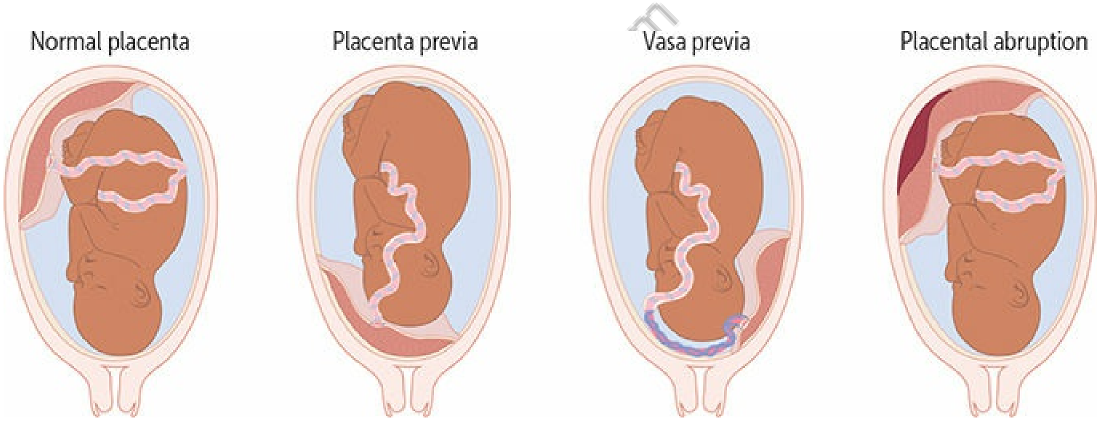

Normal placenta
Placenta previa
Vasa previa
Placental abruption

FIGURE 2.10-6. **Placental Implantation.** (Reproduced with permission from USMLE-Rx.com.)

- **Other causes:** Other forms of abnormal placentation (see later), ruptured uterus, genital tract lesions, and trauma
  - Abnormal placental implantation (Figs. 2.10-5 and 2.10-6) results from an abnormality of the decidua basalis and is an important risk factor for postpartum maternal hemorrhage.
  - Placenta accreta: Abnormal implantation of the placenta such that the placental vili are attached to the myometrium.
  - Placenta increta: Abnormal implantation of the placenta such that the placental vili penetrate into the myometrium
  - Placenta percreta: Abnormal implantation of the placenta such that the placental villi penetrate through the myometrium and into the serosa.
- ***Risk factors:*** Prior uterine incisions (C-section, fibroid removal), low-lying placentation, placenta previa, fetal Down syndrome
- ***Complications:*** Maternal hemorrhage, fetal asphyxiation, death.

KEY FACT

With third-trimester bleeding, think anatomically:

- Vagina: vaginitis, vaginal lesion/trauma
- Cervix: bloody show (labor), cervical lesion/trauma
- Placenta: Placental abruption, placenta previa
- Fetus: Fetal bleeding

MULTIPLE GESTATION

Affects 3% of all live births. Since 1980, the incidence of monozygotic (identical) twins has remained steady, whereas the incidence of dizygotic (fraternal) and higher-order births has ↑.

History/PE

Characterized by rapid uterine growth, excessive maternal weight gain, and palpation of three or more large fetal parts on Leopold maneuvers.

Diagnosis

- Ultrasonography
- β-hCG, human placental lactogen, and MSAFP elevated for GA

Treatment

- Multifetal reduction and selective fetal termination options for higher-order multiple pregnancies
- Antepartum fetal surveillance for FGR

Complications

- **Maternal:** Patients six times more likely to be hospitalized with complications of pregnancy. ↑ incidence of placenta previa and need for C-section delivery.
- **Fetal:** Twin-to-twin transfusion syndrome (most common in monochorionic twins), cord entanglement (commonly in monoamniotic twins), FGR, preterm labor, and ↑ incidence of congenital malformations.

FETAL GROWTH RESTRICTION

An EFW less than 10th percentile for GA.

History/PE

Risk factors include:

- Maternal systemic disease leading to uteroplacental insufficiency (intrauterine infection, hypertension, anemia).
- Maternal substance use.
- Placenta previa.
- Multiple gestation.
- Symmetric FGR results from aneuploidy, congenital anomalies, and intrauterine infection. This usually occurs in the first trimester.
- Asymmetric FGR ("head-sparing growth lag") results from uteroplacental insufficiency,

maternal hypertension, or other maternal chronic disease. This usually occurs in the second/third trimester.

Diagnosis

- **Best initial test:** US to confirm GA and fetal weight.
- Antepartum serial fundal height measurements with ultrasonography and weekly biophysical profiles; umbilical artery Doppler velocimetry.

Treatment

- Explore the underlying etiology and correct if possible.
- If the patient is near due date, administer steroids (eg, betamethasone) to accelerate fetal lung maturity; this treatment is required 48 hours before delivery.
- Perform antepartum fetal monitoring.
- A nonreassuring status near term may prompt delivery.

Complications

↑ perinatal morbidity and mortality.

FETAL MACROSOMIA

A birth weight >95th percentile. A common sequela of gestational diabetes due to fetal hyperglycemia.

Diagnosis

- **Best initial test:** US to estimate fetal size
- **Most accurate test:** Weighing the newborn at birth (prenatal diagnosis is imprecise)

Treatment

Consideration of planned C-section delivery for an EFW >5000 g in a pregnant patient without DM and for an EFW >4500 g in a pregnant patient with DM.

Complications

↑ risk for shoulder dystocia (leading to brachial plexus injury and Erb-Duchenne palsy) as birth weight ↑.

POLYHYDRAMNIOS

An amniotic fluid index (AFI) ≥24 or single deepest pocket ≥8 cm on ultrasonography. May be present in normal pregnancies, but fetal chromosomal developmental abnormalities must be considered.

Etiologies

- Maternal DM
- Multiple gestation
- Isoimmunization
- Pulmonary abnormalities (eg, cystic lung malformations)
- Fetal gastrointestinal (GI) tract anomalies (eg, duodenal atresia, tracheoesophageal fistula,

anencephaly)
- Twin-twin transfusion syndrome

History/PE

Usually asymptomatic.

Diagnosis

Sonographic documentation of excessive amniotic fluid volume defined as an AFI greater than or equal to (symbol) 24 cm or a single deepest pocket greater than or equal to (symbol) 8 cm. Additional evaluation should include ultrasonography for fetal anomalies, glucose testing for DM, and Rh screen. May note fundal height greater than expected for GA.

Treatment

Therapeutic serial amniocentesis to remove fluid for severe symptomatic polyhydramnios with shortness of breath; treatment of underlying cause if possible

Complications

Preterm labor, fetal malpresentation, cord prolapse

OLIGOHYDRAMNIOS

An AFI <5 on US or largest visible pocket <2 cm. Oligohydramnios is usually asymptomatic, but FGR or fetal distress may be present.

Etiologies

- Fetal urinary tract abnormalities (eg, renal agenesis, gastrourinary [GU] obstruction)
- Chronic uteroplacental insufficiency
- Postterm pregnancy (>41 weeks)
- Rupture of membranes

Diagnosis

The sum of the deepest amniotic fluid pocket in all four abdominal quadrants on ultrasonography.

Treatment

Rule out rupture of membranes. Treat the underlying cause if possible.

Complications

- Associated with a 40-fold ↑ in perinatal mortality
- Other complications: Musculoskeletal abnormalities (eg, clubfoot, facial distortion), pulmonary hypoplasia, umbilical cord compression, and FGR

RH ISOIMMUNIZATION

Fetal RBCs leak into the maternal circulation, and maternal anti-Rh IgG antibodies form that can cross the placenta, leading to hemolysis of fetal Rh⊕ RBCs (erythroblastosis fetalis; see Fig. 2.10-7). Rh isoimmunization occurs only in Rh⊖ women; ↑ risk with previous SAB or therapeutic abortion (TAB) or previous delivery with no Rho (D antigen) immune globulin given.

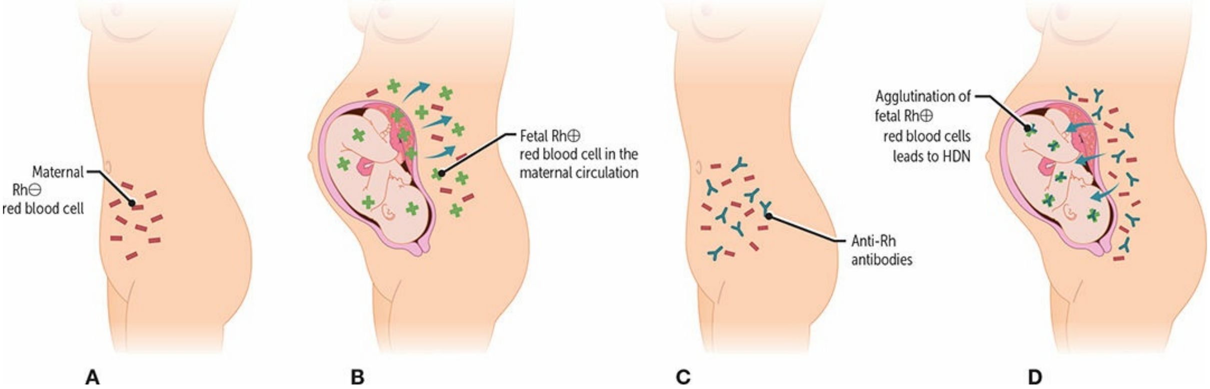

Maternal Rh⊖ red blood cell
Fetal Rh⊕ red blood cell in the maternal circulation
Anti-Rh antibodies
Agglutination of fetal Rh⊕ red blood cells leads to HDN
A
B
C
D

FIGURE 2.10-7. **Maternal antibodies, from Rh isoimmunization at the time of the previous delivery, cross the placenta and cause hemolysis of RBCs in the fetus. (A)** Rh ⊖ mother before pregnancy. **(B)** Rh ⊕ fetus in Rh ⊖ mother. **(C)** After delivery, the mother develops antibodies to Rh antigen. **(D)** Rh ⊕ fetus in the next pregnancy. *HDN*, Hemolytic disease of the newborn. (Reproduced with permission from USMLE-Rx.com.)

Diagnosis

Sensitized Rh⊖ pregnant patients with titers >1:16. Anti-D antibody titers should be closely monitored for evidence of fetal hemolysis.

Treatment

In severe cases, the physician should initiate preterm delivery. Before delivery, intrauterine blood transfusions can be given to correct a low fetal hematocrit.

Prevention

- If the patient is Rh⊖ and the other parent is Rh⊕ (or the status is unknown), give Rh immune globulin at 28 weeks.
- If the baby is Rh⊕, give the mother Rh immune globulin postpartum. The dose is based on the Kleihauer-Betke test. Inadequate dosing can lead to alloimmunization.
- Give Rh immune globulin to Rh⊖ mothers who undergo abortion or who have had an ectopic pregnancy, amniocentesis, vaginal bleeding, or placenta previa/placental abruption. Type and screening are critical.

Complications

- Hydrops fetalis when fetal hemoglobin is <7 g/dL
- Fetal hypoxia and acidosis, kernicterus, prematurity, death

ANTEPARTUM FETAL SURVEILLANCE

In general, antepartum fetal surveillance should occur in pregnancies in which the risk for antepartum fetal demise is ↑. Testing is initiated in most at-risk pregnant patients at 32 to 34 weeks (or 26–28 weeks if there are multiple worrisome risk factors). The following assessments take place:

- **Fetal movement assessment:**

  - Assessed by mother as the number of fetal movements over 1 hour
  - On average, 2 hours required for a mother to register 10 fetal movements
  - Maternal reports of ↓ fetal movements should be evaluated by means of various tests
- **NST:**
  - Performed with the mother resting in the lateral tilt position (to prevent supine hypotension)
  - Fetal heart rate (FHR) monitored externally by Doppler along with a tocodynamometer to detect uterine contractions
  - If NST nonreactive, acoustic stimulation used to wake up the fetus
  - See Table 2.10-14 for NST interpretation

TABLE 2.10-14. **Nonstress Test Interpretation**

Reactive NST (normal response)	Two accelerations in FHR over 20-minute period (see Fig. 2.10-8): - >10 bpm for 10 seconds if <32 weeks - >15 bpm for 15 seconds above baseline for >32 weeks
Nonreactive NST	Insufficient accelerations over a 40-minute period Possibility for FHR accelerations to not occur because of any of the following reasons: Fetal sleeping (most common); can use vibroacoustic stimulation to wake up fetus <32 weeks Fetal CNS anomalies Maternal sedative or narcotic administration Follow up a nonreactive stress test with contraction stress test (CST) or biophysical profile (BPP)

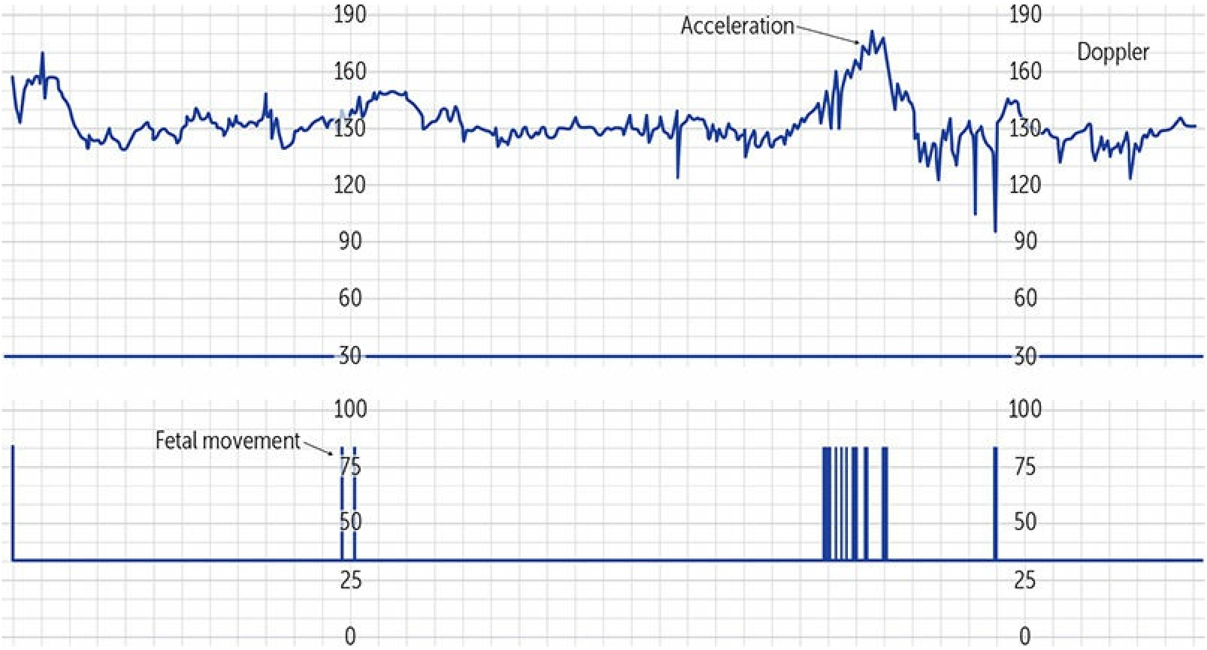


FIGURE 2.10-8. **Reactive nonstress test.** (Reproduced with permission from USMLE-Rx.com.)

- **CST:**
  - Performed in the lateral recumbent position
  - FHR monitored during spontaneous or oxytocin-induced contractions
  - Contraindicated in pregnant patients with preterm membrane rupture or known placenta previa, those with a history of uterine surgery, and in those who are at high risk for preterm labor
  - See Table 2.10-15 for CST interpretation

TABLE 2.10-15. **Contraction Stress Test Interpretation**

Positive CST	Late decelerations after 50% or more of contractions in a 10-minute window. Raises concerns about fetal compromise. Delivery is warranted.
Negative CST	No late or significant variable decelerations within 10 minutes and at least three contractions.
Equivocal CST	Intermittent late decelerations or significant variable decelerations.

- **Biophysical profile (BPP):** Uses real-time ultrasonography to assign a score of 2 (normal) or 0 (abnormal) to five parameters: fetal tone, breathing, movement, amniotic fluid volume, and NST (Table 2.10-16)

TABLE 2.10-16. **Biophysical Profile Scoring**

COMPONENT	NORMAL FINDING	SCORE
1. Nonstress test	Two accelerations ≥15 bpm lasting at least 15 seconds over a 20-minute period	2 – normal 0 – abnormal
2. Amniotic fluid volume	Single fluid pocket ≥2 × 1 cm or amniotic fluid index >5	2 – normal 0 – abnormal
3. Fetal movements	Three or more general body movements	2 – normal 0 – abnormal
4. Fetal tone	One or more episodes of flexion/extension of fetal limbs or spine	2 – normal 0 – abnormal
5. Fetal breathing movements	One or more breathing episodes ≥30 seconds	2 – normal 0 – abnormal

- **8 to 10:** Reassuring for fetal well-being
- **6:** Considered equivocal; test repeated in 24 hours if fetus <36 weeks or delivery initiated if fetus is at term
- **0 to 4:** Extremely worrisome for fetal asphyxia; strong consideration should be given to immediate delivery if no other explanation is found
- **AFI:** Sum of the measurements of the deepest cord-free amniotic fluid measured in each of the abdominal quadrants:

  - <5 cm: Oligohydramnios
  - ≥24 cm: Polyhydramnios
- **Umbilical artery Doppler velocimetry:**
  - Used only when FGR is suspected
  - Normal: High-velocity diastolic flow in the umbilical artery
  - Abnormal: Decreased, absent, or reversed end-diastolic flow in umbilical artery
  - With FGR, there is a reduction and even a reversal of umbilical artery diastolic flow
  - With oligohydramnios (AFI <5 cm), further workup is always warranted

KEY FACT

A ⊖ CST is good; a ⊕ one is bad.

MNEMONIC

When performing a BPP—

Test the Baby, MAN!

Fetal **T**one
Fetal **B**reathing
Fetal **M**ovement
Amniotic fluid volume
Nonstress test

NORMAL LABOR AND DELIVERY

DEFINITION AND STAGES OF LABOR

Labor is the process whereby contractions of the uterus are accompanied by progressive effacement (thinning) and dilation of the cervix, resulting in delivery of the fetus and placenta through the birth canal (Table 2.10-17).

TABLE 2.10-17. Stages of Labor

		DURATION		
STAGE	STARTS/ENDS	NULLIPAROUS	MULTIPAROUS	COMMENTS
First				
Latent	Onset of labor to 6-cm dilation	≤20 h	≤14 h	Prolongation seen with excessive sedation/ hypotonic uterine contractions
Active	6-cm dilation to complete cervical dilation (10 cm)	4–6 h (1.2 cm/h)	2–3 h (1.5 cm/h)	Prolongation seen with cephalopelvic disproportion
Second	Complete cervical dilation to delivery of infant	0.5–3.0 h	5–30 minutes	Neonate going through all cardinal movements of delivery
Third	Delivery of infant to delivery of placenta	0–0.5 h	0–0.5 h	Uterus contraction and placental separation to establish hemostasis
Fourth	Delivery of the placenta to 1–2 h after	1–2 h		Tone of the uterus reestablished, expelling any remaining contents Augmented by breastfeeding

KEY FACT

Braxton Hicks contractions: Irregular low-intensity contractions of the uterus without effacement or dilation of cervix.

OBSTETRIC EXAMINATION

- Leopold maneuvers are used to determine fetal lie (longitudinal or transverse) and, if possible, fetal presentation (breech or cephalic).
- **Cervical exam:**
  - Evaluate dilation, effacement, station, cervical position, and cervical consistency.
  - Confirm or determine fetal presentation.
  - Determine fetal position through palpation of the fetal sutures and fontanelles.
  - Conduct a sterile speculum exam if rupture of membranes (ROM) is suspected.

  - Determine station or engagement of the fetal head relative to a line through the ischial spines of the maternal pelvis. ⊖ station = fetal head superior to this line; ⊕ station = fetal head inferior to this line.
  - Oxytocin and misoprostol are often used as aids in the delivery process (for contraction augmentation and cervical softening).
- **Adverse Effects of Oxytocin:**
  - Hyponatremia
  - Tachysystole
  - Hypotension

FETAL HEART RATE MONITORING

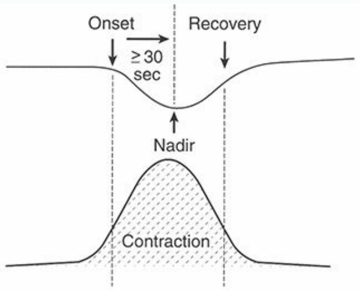
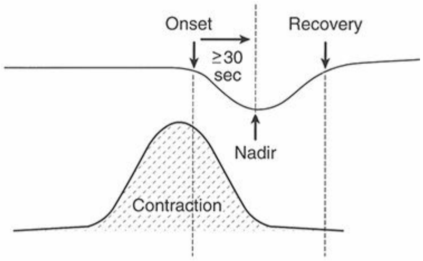
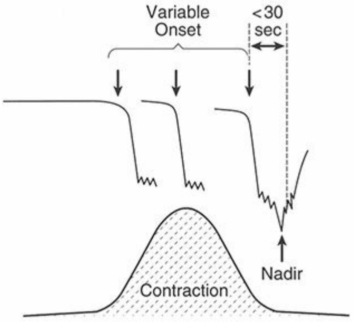
Monitoring can be performed noninvasively with Doppler US or invasively with an electrode attached to the fetal scalp (a method that yields more precise results but can only be used with ruptured membranes).

Continuous electronic FHR monitoring has not been shown to be more effective than appropriate intermittent monitoring in low-risk patients.

Components of FHR evaluation

- **Rate** (normal = 110–160 bpm)**:**
  - FHR <110 bpm: Bradycardia. Can be caused by congenital heart malformations or by severe hypoxia (secondary to uterine hyperstimulation, cord prolapse, or rapid fetal descent).
  - FHR >160 bpm: Tachycardia. Causes include hypoxia, maternal fever, intra-amniotic infection, and fetal anemia.
- **Variability:** Fluctuations in the baseline FHR that are irregular in frequency and amplitude. Related to fetal cerebral activity.
  - Absent variability: Indicates severe fetal acidemia.
  - Minimal variability: <6 bpm. Indicates fetal hypoxia or the effects of opioids, magnesium, or sleep cycle.
  - Normal variability: 6 to 25 bpm.
  - Marked variability: >25 bpm. May indicate fetal hypoxia; may occur before a ↓ in variability.
  - Sinusoidal variability: Concerning for serious fetal anemia; a pseudo-sinusoidal pattern may also occur during maternal meperidine use.
- **Accelerations:** Onset of an ↑ in FHR >15 beats above baseline to a peak in <30 seconds. Reassuring because they indicate proper function of fetal autonomic nervous system.
- **Decelerations:** See Table 2.10-18.

TABLE 2.10-18. Types of Fetal Deceleration

TYPE	DESCRIPTION	ETIOLOGY	SCHEMATIC
Early	A visually apparent, gradual (onset to nadir in >30 seconds) ↓ in FHR with a return to baseline that mirrors the uterine contraction	Head compression from the uterine contraction (normal)	
Late	A visually apparent, gradual (onset to nadir in >30 seconds) ↓ in FHR with return to baseline whose onset, nadir, and recovery occur after the beginning, peak, and end of uterine contraction, respectively	Uteroplacental insufficiency and fetal hypoxemia	
Variable	An abrupt (onset to nadir in <30 seconds), visually apparent ↓ in FHR 15 bpm below baseline lasting ≥15 seconds but <2 minutes	Umbilical cord compression	

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MNEMONIC

VEAL CHOP

Variable deceleration = **C**ord compression
Early deceleration = **H**ead compression
Accelerations = **O**K!
Late deceleration = **P**lacental insufficiency
Note: Interventions include maternal repositioning, amnioinfusion, or delivery.

OBSTETRIC ANALGESIA AND ANESTHESIA

Uterine contractions and cervical dilation result in visceral pain (T10–L1). Descent of the fetal head and pressure on the vagina and perineum result in somatic pain (pudendal nerve [S2–4]).

- **Pudendal block:**
  - Bilateral transvaginal injection of local anesthetic in and around pudendal nerve as it passes around ischial spine
  - Provides perineal anesthesia; can be used in second stage of labor
- **Epidural block:**

  - Injection of local anesthetic in epidural space that blocks lumbosacral nerve roots
  - Can be used for either vaginal delivery or C-section

Complications

- Transient hypotension from sympathetic blockade is a common complication and does not require treatment unless there are signs of shock.
- Spinal headache is another common complication if there is a dural puncture.
- Epidural anesthesia can cause postpartum urinary retention. Urethral catheterization is diagnostic and therapeutic.
- Absolute contraindications to regional anesthesia (epidural, spinal, or combination) include the following:
  - Refractory maternal hypotension
  - Maternal coagulopathy
  - Maternal use of a once-daily dose of low-molecular-weight heparin within 12 hours
  - Untreated maternal bacteremia
  - Skin infection over the site of needle placement
  - ↑ ICP caused by a mass lesion

ABNORMAL LABOR AND DELIVERY

INDICATIONS FOR C-SECTION

See Table 2.10-19 for indications. For both elective and indicated C-section deliveries, an agent such as sodium citrate, H_2 blockers, or PPIs should be used in the pregnant patient to ↓ gastric acidity and prevent acid aspiration syndrome.

TABLE 2.10-19. Indications for C-section

MATERNAL FACTORS	FETAL AND MATERNAL FACTORS	FETAL FACTORS
Prior classical C-section (vertical incision predisposes to uterine rupture with vaginal delivery)	Cephalopelvic disproportion (the most common cause of primary C-section)	Fetal malposition (eg, breech presentation, shoulder presentation)
Active genital herpes infection	Placenta previa/placental abruption	Nonreasuring fetal heart rate pattern
Cervical carcinoma	Failed operative vaginal delivery	Cord compression/prolapse
Maternal trauma/demise		
HIV infection with viral load >1000 copies/mL		
Prior transverse C-section (relative indication)		

PRETERM LABOR

Onset of labor between 20 and 37 weeks. The primary cause of neonatal morbidity and mortality.

- Risk factors include previous preterm delivery (greatest risk factor), multiple gestation, infection, ROM, uterine anomalies (eg, prior surgery, bicornuate uterus), polyhydramnios, placental abruption, poor maternal nutrition, and low socioeconomic status (SES).
- Patients found to have a short cervix at <24 weeks are at high risk for preterm labor.
- Most patients have no identifiable risk factors.

KEY FACT

Preterm labor = Regular uterine contractions + concurrent cervical change at <37 weeks.

History/PE

Presents with menstrual-like cramps, onset of low back pain, pelvic pressure, and new vaginal discharge or bleeding.

Diagnosis

- Requires the following:
  - Regular uterine contractions (three or more contractions of 30 seconds each over a 30-minute period)
  - Concurrent cervical change at <37 weeks
- Assessment for contraindications to tocolysis such as infection, nonreassuring fetal testing, and/or placental abruption
- Sterile speculum exam to rule out ROM
- Ultrasonography to rule out fetal or uterine anomalies, verify GA, and assess fetal presentation and amniotic fluid volume
- Cultures for chlamydia, gonorrhea, and group B streptococcus (GBS); also, a urinalysis (UA) and urine culture

Treatment

- Tocolytic therapy (β-agonists, $MgSO_4$, calcium channel blockers [CCBs], prostaglandin inhibitors) if <34 weeks' gestation, unless contraindicated
- Magnesium for cerebral palsy prophylaxis if <32 weeks
- Steroids to accelerate fetal lung maturity
- Penicillin or ampicillin for GBS prophylaxis if preterm delivery likely

Complications

Respiratory distress syndrome, intraventricular hemorrhage, apnea of prematurity, patent ductus arteriosus, necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, and death.

RUPTURE OF MEMBRANES

Distinguished as follows:

- **Spontaneous ROM:** Occurs after or at the onset of labor.
- **Premature ROM (PROM):** Occurs >1 hour before onset of labor. This is a variant of normal at term or may be precipitated by vaginal or cervical infections, abnormal membrane physiology, or cervical insufficient.
- **Preterm PROM (PPROM):** ROM occurring at <37 weeks.
- **Prolonged ROM:** ROM occurring >18 hours before delivery. Risk factors: Young maternal age, smoking, and sexually transmitted infections (STIs).

History/PE

Patients often report a "gush" of clear or blood-tinged amniotic fluid. Uterine contractions may be present.

Diagnosis

- Sterile speculum examination reveals pooling of amniotic fluid in the vaginal vault.
- Nitrazine paper test is ⊕ (paper turns blue, indicating alkaline pH of amniotic fluid).
- Fern test is ⊕ (a ferning pattern is seen under a microscope after amniotic fluid dries on a glass slide).
- Ultrasonography assesses amniotic fluid volume.
- If diagnosis is uncertain, ultrasonography-guided transabdominal instillation of indigo carmine dye can check for leakage (unequivocal test).
- Minimize infection risk; do not perform digital vaginal examinations on pregnant patients who are not in labor or for whom labor is not planned immediately.
- Check fetal heart tracing, maternal temperature, WBC count, and uterine tenderness for evidence of intrauterine infection.

KEY FACT

To minimize the risk for infection, limit digital vaginal examinations on women with PROM.

Treatment

- **Depends on GA:**
  - **Term:** First check GBS status and fetal presentation, then labor may be induced, or the patient can be observed for 6 hours.
  - **34 to 36 weeks:** Labor induction may be considered.
  - **<32 weeks:** Institute expectant management and hospitalization for close observation of fetal well-being and monitoring for signs of infection.
- **Antibiotics:** To prolong the latency period in the absence of infection.
- **Antenatal corticosteroids:**
  - Give betamethasone or dexamethasone for 48 hours, which **p**romote fetal lung maturity in the absence of intra-amniotic infection before 32 to 36 weeks.
- If signs of infection or fetal distress develop, the physician should give antibiotics (ampicillin and gentamicin) and induce labor.

Complications

Preterm labor and delivery, intrauterine infection, placental abruption, and cord prolapse.

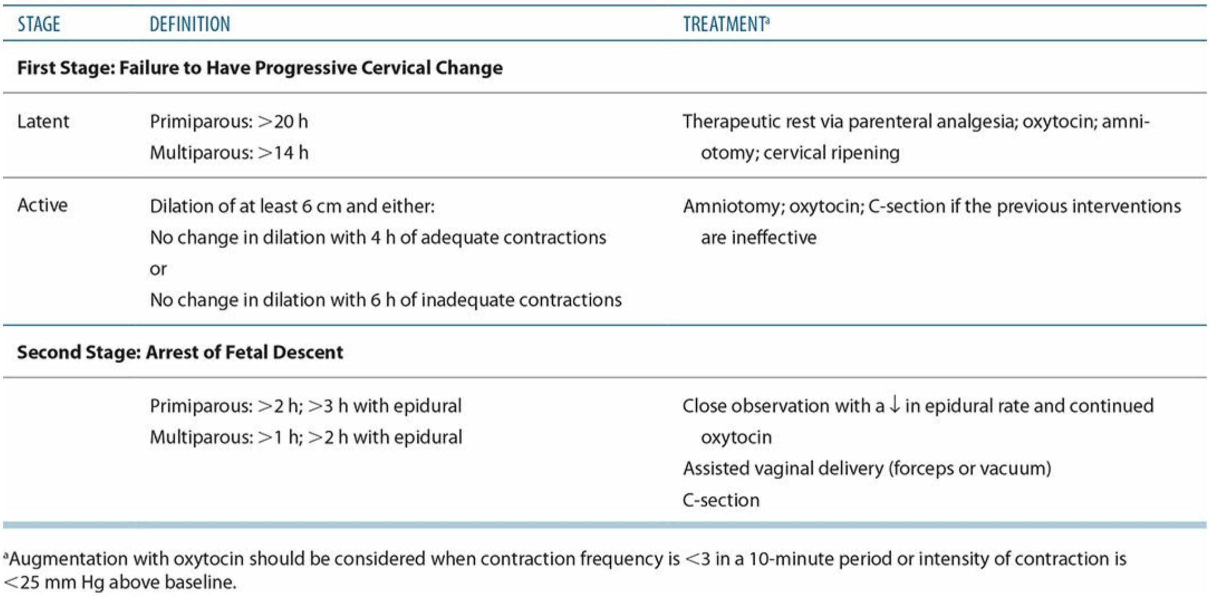
FAILURE TO PROGRESS

Associated with intrauterine infection, occiput posterior position, nulliparity, elevated birth weight, and maternal obesity.

Diagnosis

- **First-stage protraction or arrest:** Labor that fails to produce adequate rates of progressive cervical change.
- **Prolonged second stage or arrest:** Protraction or arrest of fetal descent. Most commonly caused by malposition. See Table 2.10-20 for definitions based on parity and anesthesia.

TABLE 2.10-20. Failure to Progress



STAGE	DEFINITION	TREATMENT[a]
First Stage: Failure to Have Progressive Cervical Change		
Latent	Primiparous: >20 h Multiparous: >14 h	Therapeutic rest via parenteral analgesia; oxytocin; amniotomy; cervical ripening
Active	Dilation of at least 6 cm and either: No change in dilation with 4 h of adequate contractions or No change in dilation with 6 h of inadequate contractions	Amniotomy; oxytocin; C-section if the previous interventions are ineffective
Second Stage: Arrest of Fetal Descent		
	Primiparous: >2 h; >3 h with epidural Multiparous: >1 h; >2 h with epidural	Close observation with a ↓ in epidural rate and continued oxytocin Assisted vaginal delivery (forceps or vacuum) C-section

[a] Augmentation with oxytocin should be considered when contraction frequency is <3 in a 10-minute period or intensity of contraction is <25 mm Hg above baseline.

Treatment

See Table 2.10-20.

Complications

- Intrauterine infections may lead to fetal infection, pneumonia, and bacteremia.
- The risk for postpartum hemorrhage is 11%; that of fourth-degree laceration is 3.8%.

INTRA-AMNIOTIC INFECTION

Intrauterine infections occur via ascending polymicrobial disease from the vagina through the amnion, placenta, and uterus. Less commonly, hematogenous transplacental seeding from a specific systemic maternal infection (eg, *Listeria*) can also occur. The following sections refer only to ascending infections, often called chorioamnionitis.

- ***Risk factors:*** PPROM, prolonged rupture of membranes, prolonged labor, internal fetal/uterine monitoring devices, repeated vaginal examinations
- ***Complications:*** Postpartum hemorrhage, endometritis, preterm birth, neonatal pneumonia, and encephalopathy
- ***Tx:*** Broad-spectrum IV antibiotics (ampicillin, gentamicin, clindamycin) and augmentation of labor

FETAL MALPRESENTATION

Any presentation other than vertex (ie, head closest to birth canal, chin to chest, occiput anterior). Risk factors include prematurity, prior breech delivery, uterine anomalies (eg, fibroids), polyhydramnios or oligohydramnios, multiple gestation, PPROM, hydrocephalus, anencephaly, and placenta previa.

History/PE

Breech presentations are the most common form and involve presentation of the fetal lower extremities or buttocks into the maternal pelvis (see Fig. 2.10-9). Subtypes include the following:

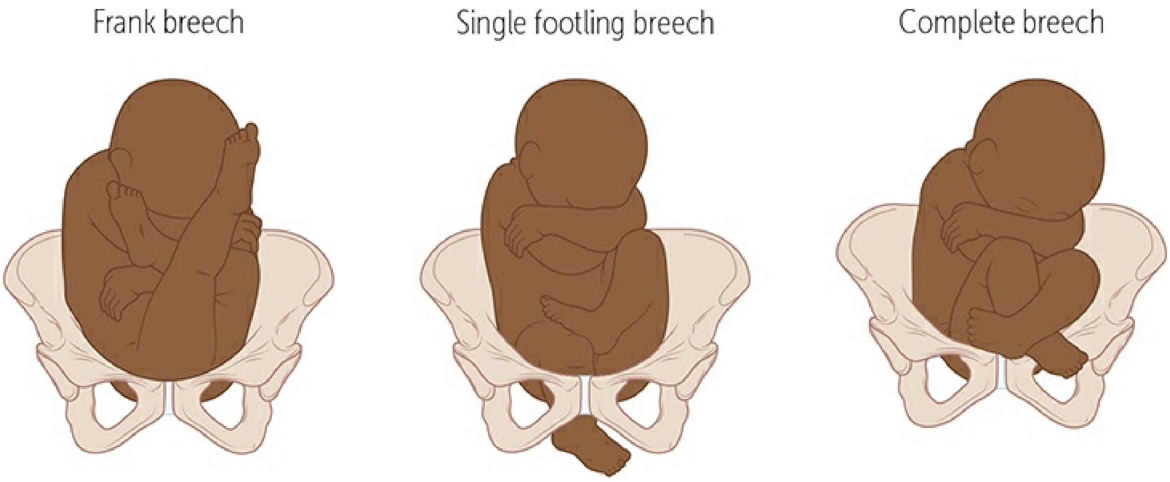


FIGURE 2.10-9. Types of breech presentations. (Reproduced with permission from USMLE-Rx.com.)

- **Frank breech (50%–75%):** The thighs are flexed, and the knees are extended.
- **Footling breech (20%):** One or both legs are extended below the buttocks.
- **Complete breech (5%–10%):** The thighs and knees are flexed.

KEY FACT

Breech presentation is the most common fetal malpresentation.

Treatment

- **Follow:** Up to 75% spontaneously change to vertex by week 38.
- **External cephalic version:** If the fetus has not reverted spontaneously, a version may be attempted by applying directed pressure to the maternal abdomen to turn the infant to vertex. The success rate is roughly 50%. Risks of version are placental abruption and cord compression, so the physician should be prepared for an emergency C-section if needed.
- **Trial of breech vaginal delivery:** Attempt trial only if delivery is imminent. Complications include cord prolapse and/or head entrapment.
- **Elective C-section:** Recommended given the lower risk for fetal morbidity.

UMBILICAL CORD PROLAPSE

Occurs when cord presents ahead of fetal parts and protrudes through cervix. Considered an obstetric emergency. Risk factors include rupturing membranes without engaged fetal head part, malpresentation, prolonged labor, and polyhydramnios.

- ***Dx:*** Visualization or palpation of the umbilical cord ahead of fetal presenting part. Can be accompanied by abrupt, severe prolonged decelerations.
- ***Tx:*** Manual elevation of presenting part, call for assistance, and preparation for emergency delivery.

SHOULDER DYSTOCIA

Affects 0.6% to 1.4% of all deliveries in the United States. Risk factors include obesity, diabetes, suspected fetal macrosomia, a history of an infant with macrosomy, postterm pregnancy, and a history of prior shoulder dystocia.

Diagnosis

Diagnosed by a prolonged second stage of labor, retraction of the head from the perineum (“turtle sign”).

Treatment

- In the event of dystocia, the following maneuvers may be attempted:
  - McRoberts maneuver (see Fig. 2.10-10)

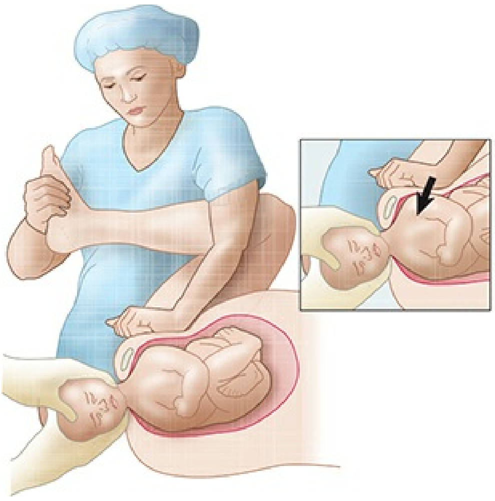


FIGURE 2.10-10. **Leg elevation (McRoberts maneuver) and application of suprapubic pressure.** Flexing the hips against the abdomen. The leg positioning illustrated here can be used to assist in a delivery where the infant is at risk for shoulder dystocia. Suprapubic pressure may cause reduction of a shoulder dystocia through adduction of the anterior shoulder. Fundal pressure should be avoided in shoulder dystocia as it may cause further impaction of the anterior shoulder against the pubic bone. (Reproduced with permission from Cunningham FG et al. *Williams Obstetrics*, 23rd ed. New York, NY: McGraw-Hill; 2010.)

  - Application of suprapubic pressure (Fig. 2.10-10)
  - Internal rotational maneuvers: Used if external maneuvers have failed to reduce the dystocia. These maneuvers reduce the diameter of the fetal shoulder girdle through abduction of the anterior shoulder toward the fetal back (Woods screw) or adduction of the anterior shoulder toward the fetal chest (Rubin) by the fingers of one hand introduced intravaginally.
  - Delivery of posterior arm
  - Intentional fracture of fetal clavicle
  - Procto-episiotomy
  - Zavanelli maneuver (manually pushing delivered fetal head into uterus and taking patient for C-section)
- Excessive traction on the fetal head to deliver the anterior shoulder can result in “stretch” injuries to the C8 to T1 brachial plexus, including Horner syndrome, Erb-Duchenne palsy, or Klumpke palsy. These brachial plexus injuries usually resolve spontaneously.

EPISIOTOMY

Surgical extension of the vaginal opening into the perineum. Can be median (midline) or mediolateral.

Complications

- **Extension to the anal sphincter (third degree) or rectum (fourth degree):** More common with midline episiotomy
- **Others:** Bleeding, infection, dyspareunia, rectovaginal fistula formation
- Routine use of episiotomy not recommended

UTERINE INVERSION

An uncommon cause of postpartum hemorrhage. This occurs when the uterine fundus prolapses through the cervix and vagina and can often be visible as a shaggy mass protruding from the vagina. The fundus is no longer palpable, and the patient is usually experiencing severe abdominal pain. Causes include excessive fundal pressure and traction on the umbilical cord. Treatment involves discontinuation of uterotonics, manually replacing the uterus, and monitoring hemodynamic status.

UTERINE RUPTURE

Very rare but life-threatening complication that may occur in pregnant patients with a history of C-section (especially vertical C-section) or other uterine surgeries. May result in postpartum bleeding. Loss of fetal station is pathognomonic for this condition, and fetal parts may be palpable in the abdomen but not in the vagina. Treatment involves emergent laparotomy.

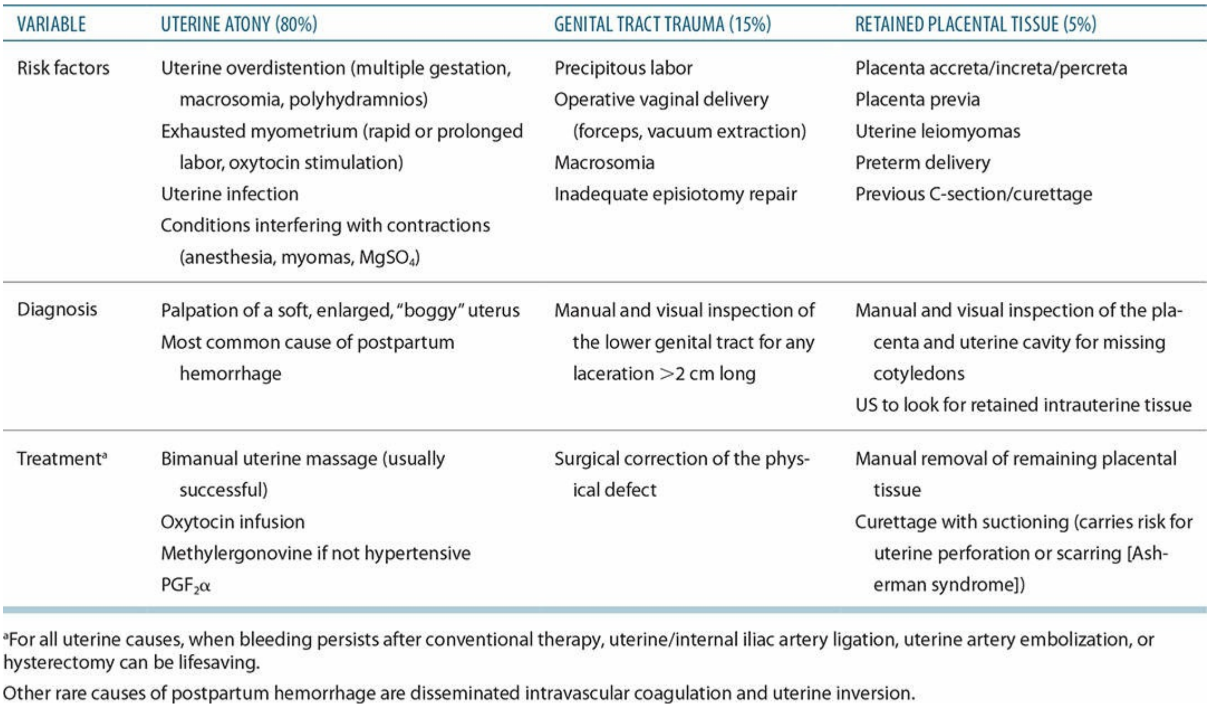
PUERPERIUM

- Normal changes after delivery include lochia (vaginal bleeding), uterine contraction, and uterine involution.
- The superficial layers of the endometrial decidua shed through the vagina for the first 3 postpartum weeks. This is called lochia.
- For the first few days, lochia is red in color (lochia rubra), and then it changes to pink in color (lochia serosa). Lochia changes to white color (lochia alba) by the end of the second week.
- Postpartum urinary retention is also common, and it is caused by bladder atony. This can be managed with catheterization and encouragement of ambulation, and it usually resolves spontaneously.
- Radiating suprapubic pain exacerbated by weight-bearing may occur because of diastasis of the pubic symphysis (separation of the pubic bones). This is more common after a traumatic delivery, and treatment is with supportive care.

POSTPARTUM HEMORRHAGE

A loss of ≥1000 mL in the first 24 hours after C-section or vaginal delivery. Table 2.10-21 summarizes common causes.

TABLE 2.10-21. **Common Causes of Postpartum Hemorrhage**



VARIABLE	UTERINE ATONY (80%)	GENITAL TRACT TRAUMA (15%)	RETAINED PLACENTAL TISSUE (5%)
Risk factors	Uterine overdistention (multiple gestation, macrosomia, polyhydramnios) Exhausted myometrium (rapid or prolonged labor, oxytocin stimulation) Uterine infection Conditions interfering with contractions (anesthesia, myomas, $MgSO_4$)	Precipitous labor Operative vaginal delivery (forceps, vacuum extraction) Macrosomia Inadequate episiotomy repair	Placenta accreta/increta/percreta Placenta previa Uterine leiomyomas Preterm delivery Previous C-section/curettage
Diagnosis	Palpation of a soft, enlarged, "boggy" uterus Most common cause of postpartum hemorrhage	Manual and visual inspection of the lower genital tract for any laceration >2 cm long	Manual and visual inspection of the placenta and uterine cavity for missing cotyledons US to look for retained intrauterine tissue
Treatment[a]	Bimanual uterine massage (usually successful) Oxytocin infusion Methylergonovine if not hypertensive $PGF_{2}\alpha$	Surgical correction of the physical defect	Manual removal of remaining placental tissue Curettage with suctioning (carries risk for uterine perforation or scarring [Asherman syndrome])

[a] For all uterine causes, when bleeding persists after conventional therapy, uterine/internal iliac artery ligation, uterine artery embolization, or hysterectomy can be lifesaving.

Other rare causes of postpartum hemorrhage are disseminated intravascular coagulation and uterine inversion.

Signs of delayed postpartum hemorrhage:

- Saturating more than one pad per hour for 2 consecutive hours
- Passing large clots
- Signs and symptoms of anemia (low hemoglobin [Hb], dizziness, lightheadedness)

Complications

- Anemia caused by chronic blood loss (predisposes to puerperal infection)
- Sheehan syndrome (discussed later)

POSTPARTUM INFECTION

A temperature ≥38°C for at least 2 of the first 10 postpartum days (not including the first 24 hours).

- ***Risk factors for postpartum endometritis:*** Emergent C-section, PROM, prolonged labor, multiple intrapartum vaginal exams, intrauterine manipulations, emergent delivery, low SES, young age, invasive fetal monitoring, prolonged ROM, bacterial colonization, and corticosteroid use.

KEY FACT

Postpartum endometritis:

- Fever >38°C
- Uterine tenderness
- Malodorous lochia

- ***Dx:*** Diagnose with blood cultures and CT, looking for a pelvic abscess.
- ***Tx:*** Broad-spectrum antibiotics and anticoagulation with heparin for 7 to 10 days.

Treatment

Broad-spectrum empiric IV antibiotics (eg, clindamycin and gentamicin) until patient has been afebrile for 48 hours (24 hours for intrauterine infections). Add ampicillin for complicated cases.

Complications

Septic pelvic thrombophlebitis:

- Pelvic infection leads to infection of the vein wall and intimal damage, leading in turn to thrombogenesis. The clot is then invaded by microorganisms.
- Suppuration follows, with liquefaction, fragmentation, and, finally, septic embolization.
- **Septic pelvic thrombophlebitis** presents with abdominal and back pain and a “picket-fence” fever curve (“hectic” fevers) with wide swings from normal to as high as 41°C (105.8°F) that does not resolve despite antibiotic treatment.
- The physician should diagnose with blood cultures and CT, looking for a pelvic abscess.
- Treatment calls for broad-spectrum antibiotics and anticoagulation with heparin for 7 to 10 days.

MNEMONIC

The seven Ws of postpartum fever (10 days postdelivery)—

Womb (endomyometritis)
Wind (atelectasis, pneumonia)
Water (UTI)
Walk (DVT, pulmonary embolism)
Wound (incision, episiotomy)
Weaning (breast engorgement, abscess, mastitis)
Wonder drugs (drug fever)

PERIPARTUM CARDIOMYOPATHY

Peripartum cardiomyopathy and hypertensive disorders of pregnancy are a rising cause of maternal mortality in high-income countries. This topic is discussed in detail in the Cardiology chapter.

SHEEHAN SYNDROME (POSTPARTUM PITUITARY NECROSIS)

Pituitary ischemia and necrosis that lead to anterior pituitary insufficiency secondary to massive obstetric hemorrhage and shock

History/PE

- The primary cause of anterior pituitary insufficiency in adult females
- Most common presenting symptom: Failure to lactate (caused by ↓ prolactin levels)
- Other symptoms: Hypotension, weakness, lethargy, cold intolerance, genital atrophy, and menstrual disorders

Diagnosis

- **Best initial test:** Adrenocorticotropic hormone (ACTH) stimulation test
- **Most accurate test:** MRI of the pituitary gland and hypothalamus to rule out tumor or other pathology

Treatment

Replacement of all deficient hormones. Some patients may recover thyroid-stimulating hormone (TSH) and even gonadotropin function after cortisol replacement alone.

LACTATION AND BREASTFEEDING

PHYSIOLOGY

- During pregnancy, ↑ estrogen and progesterone result in breast hypertrophy and inhibition of the action of prolactin on the breast.
- After delivery of the placenta, hormone levels ↓ markedly, and prolactin stimulates the alveolar epithelial cells, activating milk production. ↑ prolactin will ↓ luteinizing hormone (LH) and follicle-stimulating hormone (FSH), causing anovulation and amenorrhea during breastfeeding.
- Periodic infant suckling leads to further release of prolactin and oxytocin. Oxytocin stimulates myoepithelial cell contraction and milk ejection ("let-down reflex") and promotes greater involution of the uterus postpartum (Fig. 2.10-11).

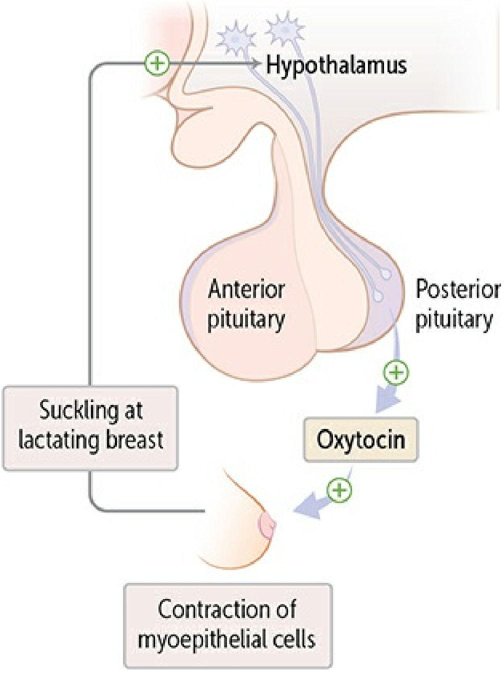

Hypothalamus
Anterior pituitary
Posterior pituitary
Suckling at lactating breast
Oxytocin
Contraction of myoepithelial cells

FIGURE 2.10-11. **Physiology of breastmilk production.** (Reproduced with permission from USMLE-Rx.com.)

- Colostrum (early breast milk) contains protein, fat, secretory IgA, and minerals.
- Within 1 week postpartum, mature milk with protein, fat, lactose, and water is produced.
- High IgA levels in colostrum provide passive immunity for the infant and protect against enteric bacteria.
- Other potential benefits of breastfeeding include the following:

  - ↓ incidence of infant allergies
  - ↓ incidence of early infant upper respiratory infections (URIs) and GI infections
  - Facilitation of mother-child bonding
  - Maternal weight loss
- Females who desire to suppress lactation should wear a supportive bra, avoid nipple stimulation, apply ice packs to the breasts, and use nonsteroidal anti-inflammatory drugs (NSAIDs) to reduce pain. Breast binding should be avoided, as it ↑ risk for mastitis.

CONTRAINDICATIONS TO BREASTFEEDING

Breastfeeding has many benefits and should be encouraged when possible. Contraindications to breastfeeding are rare (see Table 2.10-22).

TABLE 2.10-22. **Contraindications to Breastfeeding**

	INFECTIOUS	NONINFECTIOUS
Maternal	HIV (not a contraindication in resource-poor countries) Active untreated TB Active varicella Active herpes on breasts	Chemotherapy Radiation therapy Active substance use (eg, cannabis, cocaine, PCP) Certain medications (eg, tetracycline, chloramphenicol)
Infant		Galactosemia

PCP, Phencyclidine hydrochloride piperdine; *TB*, tuberculosis.

MASTITIS/BREAST ABSCESS

Cellulitis of the periglandular tissue caused by nipple trauma from breastfeeding coupled with the introduction of bacteria, usually *Staphylococcus aureus*, into the nipple ducts.

History/PE

Symptoms often begin 2 to 4 weeks postpartum, are usually unilateral, and include:

- Breast tenderness
- Erythema, edema, warmth, and possible purulent nipple drainage
- Significant fever, chills, and malaise can also be seen

Diagnosis

- Differentiate mastitis from simple breast swelling
- Infection is suggested by focal symptoms, an ↑ WBC count, and fever

Treatment

- Continuation of breastfeeding to prevent the accumulation of infected material (or use of a breast pump in patients who are no longer breastfeeding)
- Oral antibiotics (dicloxacillin, cephalexin, amoxicillin/clavulanate, azithromycin, clindamycin), antipyretics, and NSAIDs to reduce inflammation

- If no clinical improvement within 48 to 72 hours, evaluation with breast ultrasonography to assess for abscess; if present, treat abscess with incision and drainage

BREAST ENGORGEMENT

Occurs when milk production exceeds removal → bilateral firmness, fullness, tenderness, and warmth. Management calls for frequent breastfeeding, compresses (warm before and cold between feeds), and mild analgesics. If patient is not breastfeeding, management calls for suppression of lactation (described earlier).

NIPPLE INJURY

Due to poor latch/infant positioning, infection, and vasospasm. Presents with pain, bruises, cracks, blisters, and bleeding. Management with nursing technique counseling, analgesia, and compresses.

LOCALIZED PLUGGED DUCT

Stasis in milk ducts → painful, tender lump. Clinical diagnosis. Most cases resolve on their own.

GALACTOCELE

Milk retention cyst due to duct obstruction. Presents as a soft, cystic, mobile, nontender, subareolar mass on examination. Mainly clinical diagnosis. Milky fluid on fine-needle aspiration ([FNA], diagnostic and therapeutic), complex mass on US, and indeterminate or fat-fluid level on mammography (rarely indicated). Most cases resolve by themselves; treatment is usually not needed.

HIGH-YIELD FACTS IN

GYNECOLOGY

- Menarche and Normal Female Development
- Normal Menstrual Cycle
- Abnormalities of the Menstrual Cycle
  - PRECOCIOUS PUBERTY
  - PRIMARY AMENORRHEA/DELAYED PUBERTY
  - SECONDARY AMENORRHEA
  - PRIMARY DYSMENORRHEA
  - SECONDARY DYSMENORRHEA
  - ABNORMAL UTERINE BLEEDING
- Contraception
- Reproductive Endocrinology
  - CONGENITAL ADRENAL HYPERPLASIA
  - POLYCYSTIC OVARIAN SYNDROME
  - INFERTILITY
- Menopause
- Gynecologic Disorders
  - CYST AND ABSCESS OF THE BARTHOLIN DUCT
  - VAGINITIS
  - CERVICITIS
  - PELVIC INFLAMMATORY DISEASE
  - OVARIAN TORSION
  - PEDIATRIC VAGINAL DISCHARGE
  - TOXIC SHOCK SYNDROME
- Benign Breast Disorders
  - NONPROLIFERATIVE BREAST LESIONS
  - PROLIFERATIVE BREAST LESIONS WITHOUT ATYPIA
  - INTRADUCTAL PAPILLOMA
  - PHYLLODES TUMOR
  - ATYPICAL HYPERPLASIA
- Breast Cancer
- Benign Gynecologic Disorders
  - UTERINE LEIOMYOMAS (FIBROIDS)
  - NONNEOPLASTIC OVARIAN CYSTS
- Gynecologic Neoplasms
  - ENDOMETRIAL CANCER

CERVICAL CANCER
VULVAR CANCER
VAGINAL CANCER
OVARIAN CANCER

Urologic Gynecology
PELVIC ORGAN PROLAPSE

Sexual Disorders
GENITOPELVIC PAIN DISORDER (VAGINISMUS)
VULVODYNIA
FEMALE SEXUAL INTEREST/AROUSAL DISORDER

MENARCHE AND NORMAL FEMALE DEVELOPMENT

- Thelarche (breast development, onset 8–13 years of age) → pubarche (pubic hair growth) → growth acceleration → menarche (onset 10–16 years of age)
- Ages for these stages of development vary by race/ethnicity

KEY FACT

Normal male development is later in onset with a different order: testicular enlargement (onset 9–14 years of age) → penile growth → pubarche → growth acceleration → facial hair.

NORMAL MENSTRUAL CYCLE

The progression of a normal menstrual cycle is detailed here. Figure 2.11-1 shows the cyclic events in the ovary (follicular and luteal phases) and the corresponding events in the uterus (proliferative and secretory) levels throughout a typical 28-day cycle.

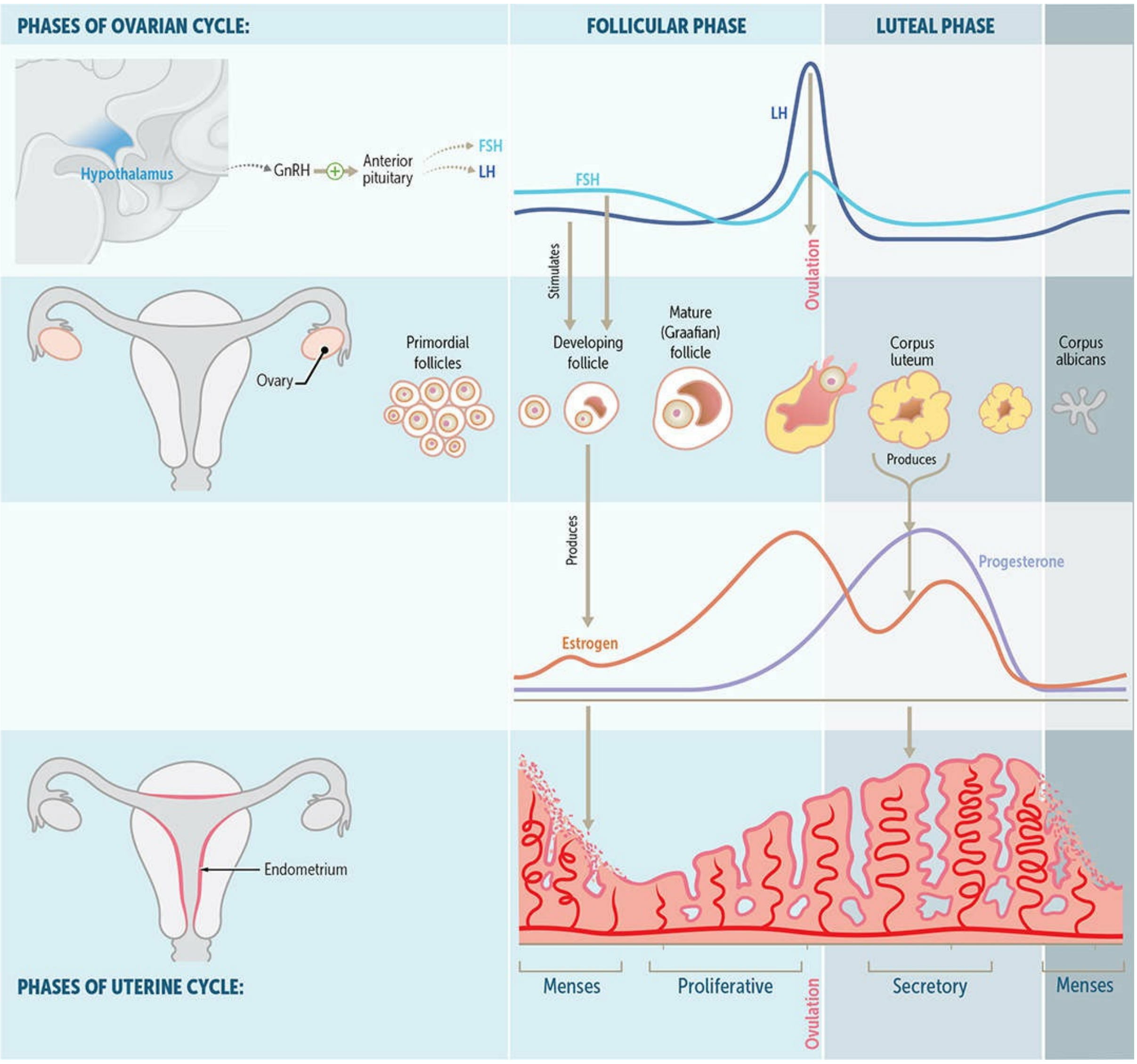

PHASES OF OVARIAN CYCLE:
FOLLICULAR PHASE
LUTEAL PHASE
Hypothalamus
GnRH
Anterior pituitary
FSH
LH
LH
FSH
Stimulates
Ovulation
Ovary
Primordial follicles
Developing follicle
Mature (Graafian) follicle
Corpus luteum
Corpus albicans
Produces
Produces
Progesterone
Estrogen
Endometrium
PHASES OF UTERINE CYCLE:
Menses
Proliferative
Ovulation
Secretory
Menses

FIGURE 2.11-1. **The phases of the ovarian and uterine cycles.** (Reproduced with permission from USMLE-Rx.com.)

Menstruation and follicular phase (days 1–13):

- Starts with menstruation and ends at luteinizing hormone (LH) surge/ovulation
- May vary but typically lasts ~13 days
- ↑ frequency of gonadotropin-releasing hormone (GnRH) pulse → ↑ follicle-stimulating hormone (FSH) → growth of follicles → ↑ estrogen production
- Results in the development of straight glands and thin secretions of the uterine lining (proliferative phase)
- By late follicular phase: Dominant follicle is selected and ↑ in size; uterine endometrium has thickened; and cervical mucus is becoming copious, thin, and stretchy

Ovulation (day 14):

- Estradiol reaches a peak → positive feedback to the pituitary gland → LH surge (smaller FSH rise) → rupture of the ovarian follicle and release of a mature ovum → travels to oviduct/uterus
- Ruptured follicular cells differentiate into the corpus luteum

KEY FACT

"LH surge" triggers ovulation and initiates production of progesterone.

Luteal phase (days 15–28):

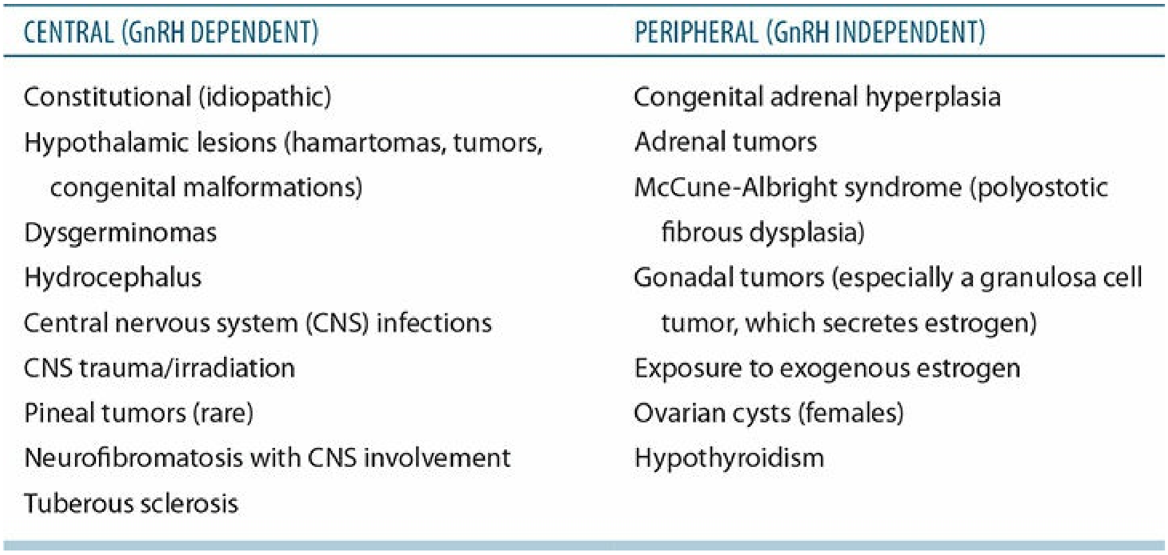
- Length of time (10–14 days) that the corpus luteum can survive without further LH or human chorionic gonadotropin (hCG) stimulation
- Change from estrogen to progesterone predominance; corpus luteum produces progesterone and some estradiol, allowing the endometrial lining to develop thick and tortuous endometrial glands with thick secretions (secretory phase)
- In the absence of fertilization and implantation, ↓ LH → ↓ progesterone and estradiol by the corpus luteum → sloughing of the endometrial lining
- With ↓ estrogen and progesterone, there is no longer negative feedback to FSH, which then increases and restarts the menstruation/follicular phase

ABNORMALITIES OF THE MENSTRUAL CYCLE

PRECOCIOUS PUBERTY

Onset of secondary sexual characteristics in a child <8 years of age. Subtypes are as follows (see Table 2.11-1):

TABLE 2.11-1. Causes of Precocious Pubertal Development



CENTRAL (GnRH DEPENDENT)	PERIPHERAL (GnRH INDEPENDENT)
Constitutional (idiopathic)	Congenital adrenal hyperplasia
Hypothalamic lesions (hamartomas, tumors, congenital malformations)	Adrenal tumors
Dysgerminomas	McCune-Albright syndrome (polyostotic fibrous dysplasia)
Hydrocephalus	Gonadal tumors (especially a granulosa cell tumor, which secretes estrogen)
Central nervous system (CNS) infections	Exposure to exogenous estrogen
CNS trauma/irradiation	Ovarian cysts (females)
Pineal tumors (rare)	Hypothyroidism
Neurofibromatosis with CNS involvement	
Tuberous sclerosis	

- **Central precocious puberty:** Early activation of hypothalamic GnRH production

KEY FACT

If onset of secondary sexual characteristics is seen before 8 years of age, work up for precocious puberty by determining bone age and conducting a GnRH stimulation test to distinguish central from peripheral precocious puberty.

- **Peripheral precocious puberty:** Results from GnRH-independent mechanisms

KEY FACT

A patient with McCune-Albright syndrome presents with precocious puberty, café au lait spots, and bony abnormalities (polyostotic fibrous dysplasia).

History/PE

- **Risk factors:** smoking, immunosuppression, HPV infection.
- Signs of estrogen excess (breast development and possibly vaginal bleeding) suggest ovarian cysts or tumors.
- Signs of androgen excess (pubic and/or axillary hair, enlarged clitoris, and/or acne) suggest adrenal tumors or congenital adrenal hyperplasia (CAH).

KEY FACT

Central precocious puberty: ↑ estradiol, ↑ LH, ↑ FSH
Peripheral precocious puberty: ↑ estradiol, ↓ LH, ↓ FSH

Diagnosis

Workup for precocious puberty includes the following:

- **Bone age:**
  - Within 1 year of chronologic age: puberty either has not started or has just begun.
  - >2 years ahead of chronologic age: puberty either started >1 year ago or recently started with rapid progression.
- **GnRH agonist (leuprolide) stimulation test:**
  - Increased LH: Central precocious puberty → CNS tumor (may be detected on MRI) vs constitutional precocious puberty.
  - No increase in LH: Peripheral precocious puberty → ovarian cyst/adrenal or gonadal tumor (may be detected on ovarian, gonadal, and/or adrenal ultrasound) vs exogenous estrogen or CAH.

Treatment

- **Central precocious puberty:** Leuprolide is first-line therapy; physical changes regress or cease to progress.
- **Peripheral precocious puberty:** The physician should treat the cause.
  - **Ovarian cysts:** No intervention is necessary, as cysts will usually regress spontaneously.
  - **Congenital adrenal hyperplasia (CAH):** Treatment with glucocorticoids. Depending on the enzyme deficiency, mineralocorticoid and sodium chloride supplementation may be necessary.
  - **Adrenal or ovarian tumors:** These require surgical resection.
  - **McCune-Albright syndrome:** Estrogen blockers such as tamoxifen or drugs that decrease estrogen synthesis such as aromatase inhibitors (eg, anastrozole) or other synthesis blockers (ketoconazole or testolactone) may be effective.

PRIMARY AMENORRHEA/DELAYED PUBERTY

Primary amenorrhea is the absence of menses by 15 years of age with secondary sexual development present. Delayed puberty is the absence of secondary sexual characteristics by 13 years of age.

History/PE

Absence of secondary sexual characteristics (no estrogen production):

- **Primary ovarian insufficiency:** Most common cause (~50%). Depletion of ovarian follicles and oocytes most commonly from Turner syndrome (45,XO). The physician should consider a history of radiation therapy and chemotherapy or gonadal dysgenesis.
- **Central hypogonadism:** Can be caused by a variety of factors, including the following:
  - Undernourishment, stress, hyperprolactinemia, or exercise
  - Central nervous system (CNS) tumor (consider prolactin-secreting pituitary adenoma if galactorrhea) or cranial irradiation
  - Kallmann syndrome (isolated gonadotropin deficiency) associated with anosmia
  - Constitutional growth delay

Presence of secondary sexual characteristics (estrogen production but other anatomic or genetic problems): Etiologies include the following:

- **Müllerian agenesis:** XX genotype with normal female testosterone levels. Absence of upper two thirds of the vagina; uterine abnormalities
- **Imperforate hymen:** Presents with hematocolpos (blood in the vagina) that cannot escape, along with a bulging hymen
- **Complete androgen insensitivity:** XY genotype with elevated testosterone levels. Presents with breast development (aromatization of testosterone to estrogen) but amenorrhea and lack of pubic hair
- **CAH:** Can present as virilization with amenorrhea or oligomenorrhea; often presents in infancy with ambiguous genitalia

PE: Pubertal development, genital exam, signs of androgen excess, physical features of Turner syndrome

KEY FACT

For Turner syndrome, think streak gonads, shield chest, amenorrhea, webbed neck, aortic coarctation, and bicuspid aortic valve.

KEY FACT

The first step in the workup of primary or secondary amenorrhea is a pregnancy test!

Diagnosis

Perform pregnancy test.

Assess for anatomic abnormalities (eg, imperforate hymen): Physical examination, ultrasonography:

- **Uterus absent:** Obtain karyotype and serum testosterone levels to assess if patient has abnormal Müllerian development (46,XX, normal female testosterone levels) or androgen insensitivity (46,XY, normal male testosterone levels).

- **Uterus present:** Check FSH, LH levels.
  - ↑ FSH: Primary ovarian insufficiency. Obtain karyotype for Turner syndrome (45,XO).
  - Normal/↓ FSH: Central hypogonadism, constitutional growth delay. Measure serum prolactin and thyrotropin, especially if galactorrhea is present.

If signs of hyperandrogenism: Consider androgen-secreting neoplasm or CAH. Check serum testosterone, dehydroepiandrosterone-sulphate (DHEAS).

If hypertensive: Evaluate for CAH (17-hydroxylase and 11-hydroxylase deficiencies).

See Table 2.11-2 for etiologies and Figure 2.11-2 for workup of primary amenorrhea.

TABLE 2.11-2. **Etiologies of Primary Amenorrhea**

	GNRH	LH/FSH	ESTROGEN/PROGESTERONE	ETIOLOGY
Constitutional growth delay	↓	↓	↓ (prepuberty levels)	Start of puberty behind schedule
Hypogonadotropic hypogonadism	↓	↓ or normal	↓	Hypothalamic or pituitary problem, low caloric intake, excessive exercise
Hypergonadotropic hypogonadism	↑	↑	↓	Ovaries have failed to produce estrogen
Anovulatory problem	↑ or ↓	Normal	↑ estrogen/↓ progesterone	Problem with estrogen receptors, immature hypothalamic-pituitary-ovarian axis (adolescents only)
Anatomic problem	Normal	Normal	Normal	Menstrual blood unable to get out

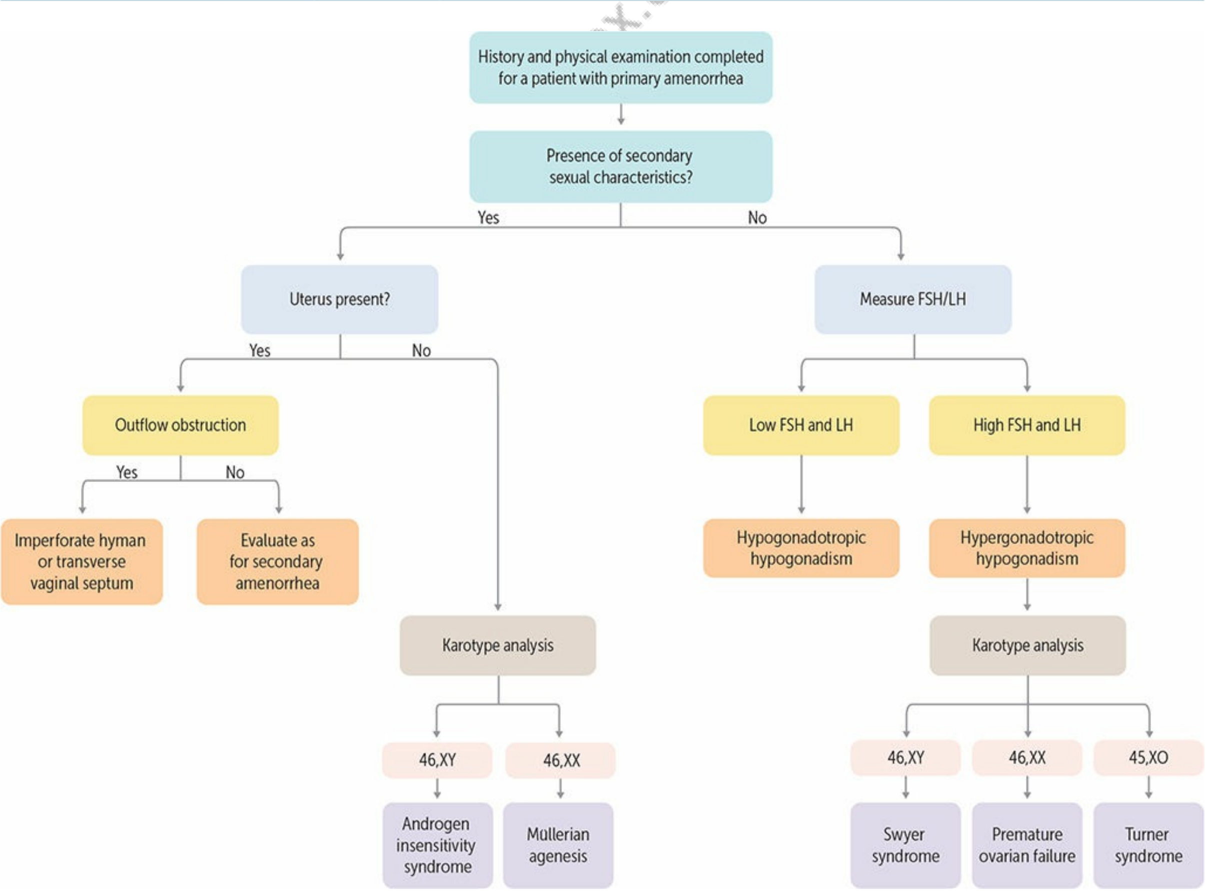

History and physical examination completed for a patient with primary amenorrhea
Presence of secondary sexual characteristics?
Yes
No
Uterus present?
Measure FSH/LH
Yes
No
Outflow obstruction
Low FSH and LH
High FSH and LH
Yes
No
Imperforate hyman or transverse vaginal septum
Evaluate as for secondary amenorrhea
Hypogonadotropic hypogonadism
Hypergonadotropic hypogonadism
Karotype analysis
Karotype analysis
46,XY
46,XX
46,XY
46,XX
45,XO
Androgen insensitivity syndrome
Mullerian agenesis
Swyer syndrome
Premature ovarian failure
Turner syndrome

FIGURE 2.11-2. **Workup of primary amenorrhea.** (Reproduced with permission from USMLE-Rx.com.)

Treatment

- **Constitutional growth delay:** No treatment is necessary.
- **Hypogonadism:** Begin hormone replacement therapy (HRT) with estrogen alone at the lowest dose. Begin cyclic estrogen/progesterone therapy 12 to 18 months later (if the uterus is present).
- **Anatomic:** Requires surgical intervention.

SECONDARY AMENORRHEA

The absence of menses for 6 consecutive months in females who have passed menarche. Etiologies include:

- Pregnancy
- **Ovary:** Polycystic ovarian syndrome (PCOS), premature ovarian insufficiency, chemotherapy, radiation
- **Hypothalamus:** Neoplasm, functional hypothalamic amenorrhea (poor nutrition, exercise, and stress), systemic illness (type 1 diabetes mellitus [DM], celiac disease)
- **Pituitary gland:** Adenoma (eg, prolactin secreting), sellar masses, Sheehan syndrome
- **Thyroid gland:** Hypothyroidism, hyperthyroidism
- **Uterus:** Asherman syndrome, cervical stenosis

Diagnosis

- History and physical examination
- Exclusion of pregnancy with a pregnancy test
- If ⊖, measurement of FSH, thyroid-stimulating hormone (TSH), and prolactin
  - ↑ FSH indicates primary ovarian insufficiency.
  - ↑ TSH indicates hypothyroidism.
  - ↑ prolactin (inhibits the release of GnRH and thus LH and FSH) points to a pituitary pathology. An MRI of the pituitary gland should be ordered to look for a prolactin-secreting pituitary adenoma.
- Initiation of a progestin challenge (10 days of progestin). See Figure 2.11-3 for an algorithm of the diagnostic workup.

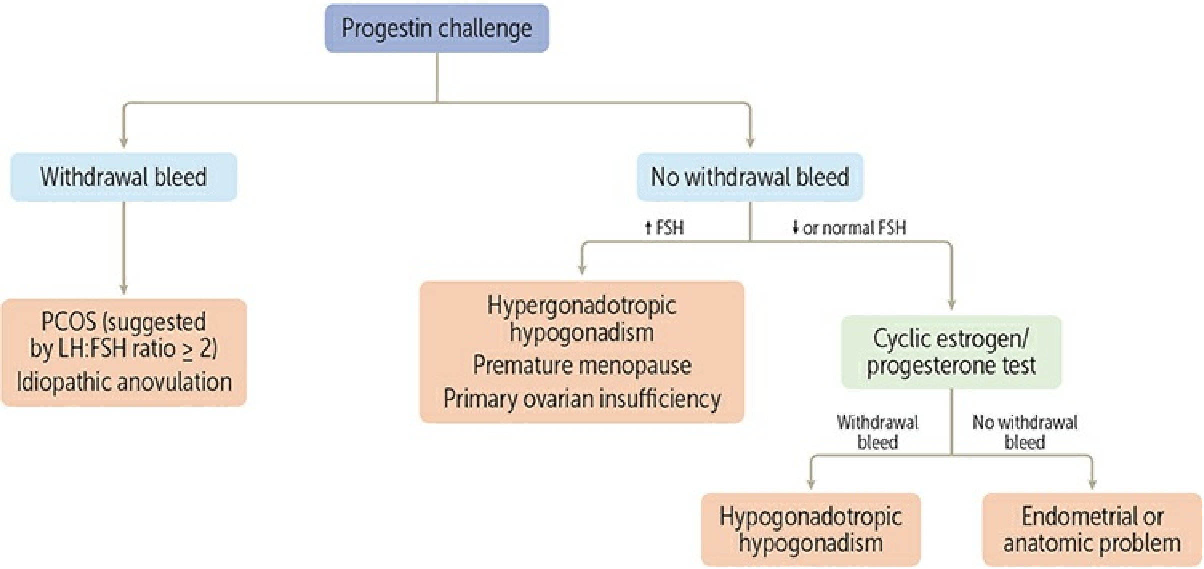

Progestin challenge
Withdrawal bleed
No withdrawal bleed
PCOS (suggested by LH:FSH ratio ≥ 2)
Idiopathic anovulation
↑ FSH
↓ or normal FSH
Hypergonadotropic hypogonadism
Premature menopause
Primary ovarian insufficiency
Cyclic estrogen/ progesterone test
Withdrawal bleed
No withdrawal bleed
Hypogonadotropic hypogonadism
Endometrial or anatomic problem

FIGURE 2.11-3. Workup of secondary amenorrhea. (Reproduced with permission from USMLE-Rx.com.)

  - ⊕ **progestin challenge (withdrawal bleed):** Anovulation that is probably caused by noncyclic gonadotropin secretion, pointing to PCOS or idiopathic anovulation
  - ⊖ **progestin challenge (no bleed):** Uterine abnormality or estrogen deficiency
- **Signs of hyperglycemia (polydipsia, polyuria) or hypotension:** A 1-mg overnight dexamethasone suppression test to distinguish CAH (21-hydroxylase deficiency), Cushing syndrome, and Addison disease

Q

A 16-year-old girl presents with ↓ appetite, insomnia, and amenorrhea for 3 months. What is the most likely diagnosis, and how should the physician confirm it?

- **Clinical hyperandrogenism:** If present, check testosterone, DHEA-S, and 17-hydroxyprogesterone levels
  - **Mild pattern:** PCOS, CAH, or Cushing syndrome
  - **Moderate-to-severe pattern** (virilization, eg, deepening voice, male pattern baldness, clitoromegaly)**:** Concerning for ovarian or adrenal tumor

KEY FACT

- Hirsutism = Male hair pattern (hair in face, chest, back)
- Virilization = male pattern baldness (frontal balding), muscularity, clitoromegaly, and deepening of the voice
- Defeminization = ↓ breast size; loss of feminine adipose tissue

Treatment

- **Hypothalamic-pituitary-ovarian axis:** Reversal of underlying cause. Induction with fertility medications if trying to conceive. If not, use oral contraceptives.
- **Tumors:** Excision; medical therapy for prolactinomas (eg, cabergoline, bromocriptine).
- **Premature ovarian insufficiency** (<40 years of age): If the uterus is present, treatment with combined oral contraceptives or estrogen plus progestin replacement therapy.

PRIMARY DYSMENORRHEA

Menstrual pain associated with ovulatory cycles in the absence of pathologic findings. Caused by uterine vasoconstriction, anoxia, and sustained contractions mediated by an excess of prostaglandin $F_2\alpha$ ($PGF_2\alpha$).

History/PE

- Presents with low, midline, spasmodic pelvic pain that often radiates to the back or inner thighs
- Cramps that occur in the first 1 to 3 days of menstruation possibly associated with nausea, diarrhea, headache, and flushing
- No pathologic findings on pelvic examination

Diagnosis

A diagnosis of exclusion. Rule out secondary dysmenorrhea (see next section).

Treatment

Nonsteroidal anti-inflammatory drugs (NSAIDs), topical heat therapy, combined hormonal contraception, progestin intrauterine device (IUD).

SECONDARY DYSMENORRHEA

Menstrual pain for which an organic cause exists. Common causes include endometriosis, adenomyosis, fibroids, adhesions, and pelvic inflammatory disease (PID).

History/PE

- Patients may have a palpable uterine mass, cervical motion tenderness, adnexal tenderness, or vaginal or cervical discharge. However, normal abdominal and pelvic exams do not rule out pathology.
- See Table 2.11-3 for distinguishing features of endometriosis vs adenomyosis.

TABLE 2.11-3. Endometriosis vs Adenomyosis

VARIABLE	ENDOMETRIOSIS	ADENOMYOSIS
Definition	Functional endometrial glands and stroma outside the uterus	Endometrial tissue in the myometrium of the uterus
History/PE	Cyclic pelvic and/or rectal pain and dyspareunia Uterus is not enlarged but on exam may be fixed in place; tender nodules may be palpated in posterior cul-de-sac	Classic triad of pain; heavy menstrual bleeding; and an enlarged, boggy, symmetric uterus
Diagnosis	Endometriosis requires direct visualization by laparoscopy or laparotomy with tissue biopsy Classic lesions have a blue-black ("raspberry") or dark brown ("powder-burned") appearance The ovaries may have endometriomas ("chocolate cysts")	MRI can aid in diagnosis but can be costly Ultrasonography is useful but cannot always distinguish between leiomyoma and adenomyosis Ultimately, adenomyosis is a pathologic diagnosis
Treatment	Pharmacologic: Inhibition of ovulation; combination hormonal contraception (first-line), GnRH analogues (leuprolide), danazol, NSAIDs, or progestins Conservative surgical treatment: Excision, cauterization, or ablation of the lesions and lysis of adhesions Definitive surgical treatment: Hysterectomy/bilateral salpingo-oophorectomy (TAH/BSO) ± lysis of adhesions	Pharmacologic: Largely symptomatic relief; NSAIDs (first-line) plus combined hormonal contraception or progestins Conservative surgical treatment: Endometrial ablation; however, complete eradication of deep adenomyosis is difficult and usually results in treatment failure Definitive surgical treatment: Hysterectomy is the only definitive treatment
Complications	Infertility (the most common cause among menstruating women >30 years of age)	Abnormal uterine bleeding, painful menses

Diagnosis

- Obtain a β-hCG test to exclude ectopic pregnancy.
- Perform a pelvic examination to assess uterine size, tenderness, and consistency and to evaluate for ovarian masses.

A

The most likely diagnosis is pregnancy. It can be confirmed with a β-human chorionic gonadotropic (β-hCG) test.

- Order the following:
  - Complete blood cell (CBC) count with differential to rule out infection
  - Urinalysis (UA) to rule out urinary tract infection (UTI)
  - Gonococcal/chlamydial swabs to rule out sexually transmitted diseases (STDs)/PID
- Consider ultrasound to assess endometrium, uterus, and ovaries (look for pelvic pathology causing pain [see Table 2.11-3]).

KEY FACT

Polyps are not associated with pain.

Treatment

Treatment is etiology specific.

Q

A 28-year-old woman presents for a wellness exam. She reports that approximately 2 weeks after her menses, she experiences intense, sharp lower quadrant abdominal pain that lasts a couple of hours. The pain varies from the right to the left side each cycle. What is the name of this phenomenon?

ABNORMAL UTERINE BLEEDING

- Normal menstrual bleeding ranges from 2 to 7 days. Abnormal uterine bleeding (AUB) refers to alterations in quantity, duration, or frequency. Classified by the acronym PALM-COEIN.
  - **PALM** refers to structural causes—**P**olyp, **A**denomyosis, **L**eiomyoma, and **M**alignancy/hyperplasia.
  - **COEIN** refers to nonstructural causes—**C**oagulopathy, **O**vulatory dysfunction, **E**ndometrial, **I**atrogenic, and **N**ot yet classified.

KEY FACT

Postmenopausal vaginal bleeding is cancer until proven otherwise.

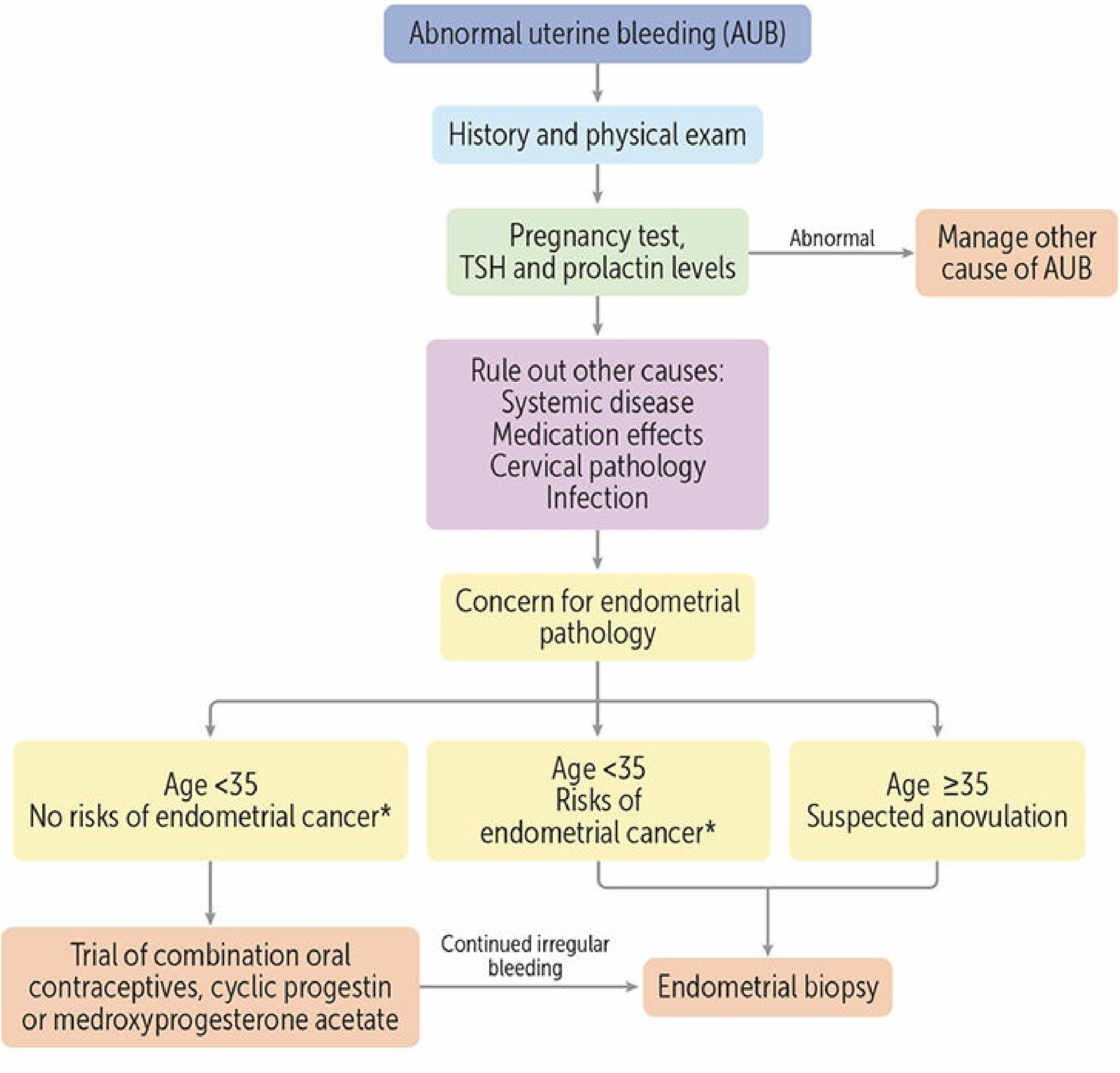
History/PE

- **Assess the extent of bleeding:**
  - **Oligomenorrhea:** An ↑ length of time between menses (35–90 days between cycles)
  - **Polymenorrhea:** Frequent menstruation (<21-day cycle)
  - **Heavy menstrual bleeding (previously termed menorrhagia):** ↑ amount of flow

  (>80 mL of blood loss per cycle) or prolonged bleeding (flow lasting >8 days). Heavy menstrual bleeding may lead to anemia.
  - **Intermenstrual bleeding (previously termed metrorrhagia):** Bleeding between periods.
  - **Heavy prolonged menstrual bleeding (previously termed menometrorrhagia):** Excessive and irregular bleeding.
- On pelvic examination, the physician should evaluate the uterus and the cervix for a potential etiology of the bleeding. An enlarged uterus may be suggestive of pregnancy or uterine myomas. A cervical mass or other cervical abnormalities are concerning for cervical malignancy, infection, or an endocervical or prolapsed endometrial polyp.

Diagnosis

- β-hCG test to rule out pregnancy
- CBC to evaluate for anemia
- Pap smear to rule out cervical cancer
- Gonorrhea/chlamydia probe to rule out cervical bleeding from cervicitis
- Thyroid function tests and prolactin to rule out hyperthyroidism/hypothyroidism and hyperprolactinemia
- Platelet count, prothrombin time (PT)/partial thromboplastin time (PTT) to rule out von Willebrand disease and factor XI deficiency, primarily in adolescent patients
- Ultrasonography to look for uterine masses and polycystic ovaries and to assess thickness of the endometrium
- **Indications for an endometrial biopsy:**
  - If the endometrium is ≥4 mm in a postmenopausal woman or if the patient is >45 years of age.
  - If the patient is >35 years of age with risk factors for endometrial hyperplasia (eg, obesity, diabetes).
- See Figure 2.11-4 for guidance on which premenopausal patients should have an endometrial biopsy as part of their workup for AUB.

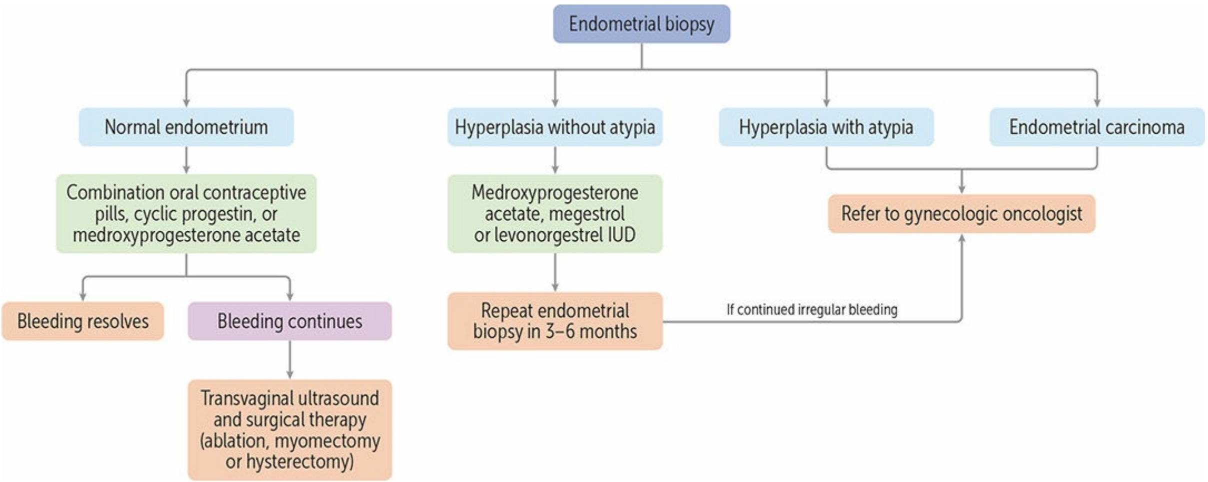


Abnormal uterine bleeding (AUB)
History and physical exam
Pregnancy test, TSH and prolactin levels
Abnormal
Manage other cause of AUB
Rule out other causes: Systemic disease Medication effects Cervical pathology Infection
Concern for endometrial pathology
Age <35 No risks of endometrial cancer*
Age <35 Risks of endometrial cancer*
Age ≥35 Suspected anovulation
Trial of combination oral contraceptives, cyclic progestin or medroxyprogesterone acetate
Continued irregular bleeding
Endometrial biopsy

*Risk factors for endometrial cancer: chronic anovulatory cycles, obesity, nulliparity, diabetes mellitus, tamoxifen therapy

FIGURE 2.11-4. **Evaluation of abnormal uterine bleeding.** (Reproduced with permission from USMLE-Rx.com.)

- See Figure 2.11-5 for guidance on management of endometrial biopsy results.



Endometrial biopsy
Normal endometrium
Hyperplasia without atypia
Hyperplasia with atypia
Endometrial carcinoma
Combination oral contraceptive pills, cyclic progestin, or medroxyprogesterone acetate
Medroxyprogesterone acetate, megestrol or levonorgestrel IUD
Refer to gynecologic oncologist
Bleeding resolves
Bleeding continues
Repeat endometrial biopsy in 3–6 months
If continued irregular bleeding
Transvaginal ultrasound and surgical therapy (ablation, myomectomy or hysterectomy)

FIGURE 2.11-5. **Management of endometrial biopsy results.** (Reproduced with permission from

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A

This is called mittelschmerz, pain at ovulation caused by progesterone production. It can switch sides, depending on which ovary ovulates in a given cycle.

Treatment

Acute heavy bleeding:

- High-dose estrogen intravenously stabilizes the endometrial lining and typically stops bleeding within 1 hour. When bleeding stabilizes, the physician can transition patient to combined oral contraceptive or add progestin.
- If estrogen is contraindicated, the physician can give high-dose progestin therapy alone.
- If bleeding is not controlled within 12 to 24 hours, dilation and curettage (D&C) may be indicated.

Ovulatory bleeding (excessive bleeding associated with normal menstrual cycles):

- NSAIDs ↓ blood loss.
- Tranexamic acid can be given for 5 days during menses.
- If the patient is hemodynamically stable, the physician can prescribe oral contraceptive pills (OCPs), oral or injectable progestin, or insertion of a progestin IUD.

KEY FACT

For acute life-threatening AUB:

- IV estrogen best for adolescent/younger patients
- Consider surgical management (D&C) as first-line treatment for patients >45 years of age for whom thorough endometrial sampling is indicated and/or in whom the cardiovascular risk of systemic intravenous (IV) estrogen is high.

Anovulatory bleeding:

- Goal: Convert proliferative endometrium to secretory endometrium (to ↓ the risk for endometrial hyperplasia/cancer)
- Progestins for 10 days to stimulate withdrawal bleeding
- Combined hormonal contraception
- Progestin IUD

KEY FACT

Combined hormonal contraception and the progesterone-containing IUD are highly effective treatment options for non-life-threatening menorrhagia.

If medical management fails:

- D&C

- Hysteroscopy to identify endometrial polyps or to perform directed uterine biopsies
- Uterine artery embolization, hysterectomy, or endometrial ablation appropriate for females:
  - For whom hormonal treatment fails
  - Who no longer desire fertility
  - Who have symptomatic anemia and/or who experience a disruption in their quality of life from persistent, unscheduled bleeding

KEY FACT

Complications of AUB include anemia. Presence of AUB raises concern for underlying endometrial hyperplasia and/or carcinoma.

Contraception

Eighty-five percent of sexually active women with no contraception will become pregnant within 1 year. Table 2.11-4 describes the effectiveness of contraceptive methods along with their relative advantages and disadvantages. See Table 2.11-5 for contraindications to common methods of contraception. Emergency contraception (EC) methods prevent pregnancy after unprotected sex or contraceptive failure. Table 2.11-6 describes the various methods of EC.

TABLE 2.11-4. Contraceptive Methods

METHOD	MECHANISM	ADVANTAGES	DISADVANTAGES
MOST EFFECTIVE: >99%			
Copper intrauterine device (IUD)	Foreign body results in inflammation; copper has a spermicidal effect	Effective for up to 10 years Immediate fertility once removed No hormonal exposure Safe with breastfeeding	↑ cramping and heavier bleeding (5%–10%) Risk for uterine perforation (1/100) ↑ risk for ectopic pregnancy (rare)
Implant (progestin-only implant)	Inhibits ovulation; ↑ cervical mucus viscosity	Effective for up to 3 years Immediate fertility once removed Safe with breastfeeding Lighter periods	Irregular periods, scarring at site of insertion (upper arm)
IUD with progestin	Progesterone leads to cervical mucus thickening and endometrial decidualization	Effective for 3–8 years depending on type of P4-IUD Immediate fertility once removed Safe with breastfeeding Lighter periods; less cramping	Spotting (up to 6 months), acne Risk for uterine perforation (1/100) ↑ risk for ectopic pregnancy (rare)
Surgical sterilization (vasectomy, tubal ligation)		Permanently effective; safe with breastfeeding	Tubal ligation: Irreversible; ↑ risk for ectopic pregnancy (rare) Vasectomy: Most failures result from not waiting for two ⊖ semen samples
VERY EFFECTIVE: 90%–99%			
OCPs (combination estrogen and progestin)	Inhibit FSH/LH, suppressing ovulation; thicken cervical mucus; decidualize endometrium	↓ risk for ovarian and endometrial cancers[a] Predictable, lighter, less painful menses Can improve acne	Requires daily compliance Breakthrough bleeding (10%–30%) Thromboembolism risk (especially in smokers >35 years of age) Cannot be used in patients of any age who have migraines with aura HTN, gastroesophageal reflux disease (progesterone relaxes the lower esophageal sphincter)
Transdermal patch ("the patch")	Same as OCPs	Predictable, lighter, less painful menses Weekly administration	Thromboembolism risk (especially in smokers >35 years of age, patients with chronic hypertension [HTN])
Vaginal ring	Same as OCPs	Can make periods more regular Can be placed intravaginally for 3 weeks; removed for 1 week (menses will occur during this time)	May ↑ vaginal discharge Spotting (first 1–2 months) Thromboembolism risk (especially in smokers >35 years of age, patients with chronic HTN)
Medroxyprogesterone	Intramuscular (IM) injection (progestin) Suppresses ovulation and decidualizes endometrium	Lighter or no periods Each shot works for 3 months	Irregular bleeding, weight gain Decreases in bone mineral density ([BMD], reversible) Delayed fertility after discontinuation (up to 10 months)
Progestin-only "minipills"	Thicken cervical mucus	Safe with breastfeeding	Requires strict compliance with daily timing

METHOD	MECHANISM	ADVANTAGES	DISADVANTAGES
MODERATELY EFFECTIVE: 75%–90%			
Male condoms	A latex sheath covering the penis	The only method that effectively protects against pregnancy and STDs, including HIV	Possible allergy to latex or spermicides
Diaphragm with spermicide	A barrier inserted over the cervix to prevent entry of sperm	Some protection against STDs	Must be fitted by the provider
Female condom	A barrier sheath that is inserted into the vagina	Some protection against STDs	Can be difficult to use
Fertility awareness methods (natural family planning)	Sexual intercourse is avoided on days during the menstrual cycle on which conception is likely (near the time of ovulation)	No adverse effects	Not reliable for patients with irregular menses Requires close monitoring of ovulation indicators (cervical mucus, basal body temperature, cycle length) No STD/HIV protection
LESS EFFECTIVE: 68%–74%			
Withdrawal	Removal of the penis before ejaculation	No adverse effects	No STD/HIV protection Not recommended as a primary method
Spermicide	A substance that inhibits sperm motility	May be used as a secondary method	Not recommended as a primary method

[a] Other combined hormonal methods (eg, patch, ring) may also protect against endometrial and ovarian cancers; however, data are still lacking, given their relatively recent introduction.

TABLE 2.11-5. **Contraindications to Common Methods of Contraception**

ESTROGEN-CONTAINING HORMONAL METHODS[a]	IUDS (PROGESTERONE AND COPPER)
Pregnancy/breastfeeding History of stroke, hypertension, deep venous thrombosis/pulmonary embolism Unexplained vaginal/uterine bleeding Estrogen-dependent (eg, breast) cancer Benign or malignant liver neoplasm Abnormal liver function Current tobacco use and >35 years of age Migraine with visual aura Diabetic retinopathy or neuropathy	Severe uterine structural abnormality (bicornuate, septate) Known or suspected pregnancy Active gynecologic infection (within 3 months) Unexplained vaginal/uterine bleeding Suspected gynecologic malignancy Copper IUD alone: ▪ Copper intolerance (allergy, Wilson disease) ▪ Severe dysmenorrhea and/or menorrhagia Progestin IUD alone: ▪ Levonorgestrel allergy ▪ Breast cancer ▪ Acute liver disease or liver tumor

[a] Includes OCPs, vaginal ring, and transdermal patch.

TABLE 2.11-6. Emergency Contraceptive Methods

METHOD AND MECHANISM	ADVANTAGES	DISADVANTAGES[a]
Ulipristal: Selective progesterone receptor antagonist; delays ovulation; can be used up to 120 hours after intercourse	Does not disrupt embryo postimplantation Safe for all patients Very effective Can be used in active pelvic infection Can be used longer after intercourse More effective due to 2 mechanisms of action Preferred in patients with higher BMI	Expensive Requires a prescription
Levonorgestrel: A progestin-only pill that delays ovulation; must be used within 72 hours of intercourse	Fewer nausea/vomiting adverse effects than an oral contraceptive taper Available without a prescription	Less effective than other methods Shorter window after intercourse for efficacy
Oral contraceptive taper: Delays ovulation; most effective within 72 hours of intercourse but can be used up to 120 hours after intercourse	Useful for patients who have OCPs at home	Nausea, vomiting, fatigue, headache, dizziness, breast tenderness Requires a prescription
Copper IUD: Copper particles disrupt sperm and ovum function, preventing fusion; may prevent implantation; can be used up to 7 days after intercourse	The most effective emergency contraceptive method (99% effective) Can be used as emergency contraceptive and continued for up to 10 years of contraception	High initial cost of insertion Must be inserted by the provider Should test for pregnancy and STIs before insertion Cannot be placed during active infection

[a] None of these methods provides protection from or treatment for HIV or other sexually transmitted infections.

KEY FACT

Multiple sexual partners and nulliparity are not absolute contraindications to IUD use.

KEY FACT

Combined hormonal methods of contraception decrease the risk for endometrial and ovarian cancers.

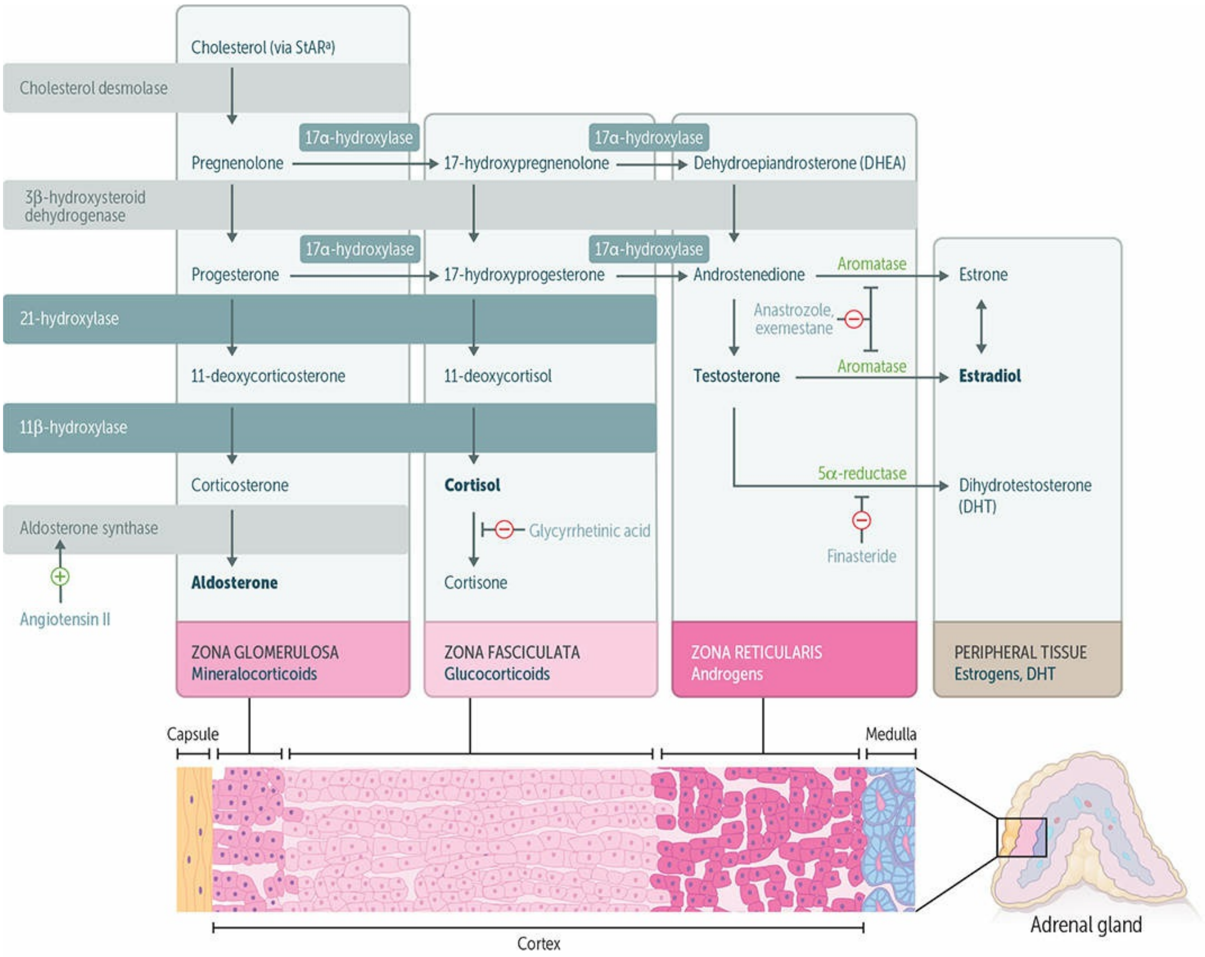
REPRODUCTIVE ENDOCRINOLOGY

KEY FACT

In CAH, .if the first number in the name of the deficient enzyme is a 1, it is associated with hypertension. If the second number is a 1, it is associated with hyperandrogenism.

CONGENITAL ADRENAL HYPERPLASIA

CAH is a deficiency of at least one enzyme required for the biochemical synthesis of cortisol from cholesterol (see Fig. 2.11-6 and Table 2.11-7). Includes the following:


Cholesterol (via StARa)
Cholesterol desmolase
17α-hydroxylase
17α-hydroxylase
Pregnenolone
17-hydroxypregnenolone
Dehydroepiandrosterone (DHEA)
3β-hydroxysteroid dehydrogenase
17α-hydroxylase
17α-hydroxylase
Progesterone
17-hydroxyprogesterone
Androstenedione
Aromatase
Estrone
21-hydroxylase
Anastrozole, exemestane
11-deoxycorticosterone
11-deoxycortisol
Testosterone
Aromatase
Estradiol
11β-hydroxylase
5α-reductase
Corticosterone
Cortisol
Dihydrotestosterone (DHT)
Aldosterone synthase
Glycyrrhetinic acid
Finasteride
Aldosterone
Cortisone
Angiotensin II
ZONA GLOMERULOSA
Mineralocorticoids
ZONA FASCICULATA
Glucocorticoids
ZONA RETICULARIS
Androgens
PERIPHERAL TISSUE
Estrogens, DHT
Capsule
Medulla
Adrenal gland
Cortex

*StAR: Steroidogenic acute regulatory protein. Rate limiting step in steroid synthesis.

FIGURE 2.11-6. **Glucocorticoid biosynthesis pathway.** (Modified with permission from USMLE-Rx.com.)

TABLE 2.11-7. **Overview of Congenital Adrenal Hyperplasia**

ENZYME DEFICIENCY	MINERALOCORTICOIDS	CORTISOL	SEX HORMONES	BP	[K+]	LABS	PRESENTATION
17α-hydroxylase[a]	↑	↓	↓	↑	↓	↓androstenedione	XY: Ambiguous genitalia, undescended testes XX: Lacks secondary sexual development
21-hydroxylase[a]	↓	↓	↑	↓	↑	↑ renin activity ↑ 17-hydroxyprogesterone	Most common Presents in infancy (salt wasting) or childhood (precocious puberty) XX: Virilization
11β-hydroxylase[a]	↓ aldosterone ↑ 11-deoxycorticosterone (results in ↑ BP)	↓	↑	↑	↓	↓ renin activity	XX: Virilization

[a] All congenital adrenal enzyme deficiencies are characterized by an enlargement of both adrenal glands and hyperpigmentation caused by ↑ ACTH stimulation (caused by ↓ cortisol).

Modified with permission from Le T et al. *First Aid for the USMLE Step 1 2022.* New York, NY: McGraw-Hill; 2022.

- **21-Hydroxylase deficiency:** Accounts for ~90% of CAH cases. “Classic” form is most severe and presents as a newborn female with ambiguous genitalia and adrenal insufficiency (with or without life-threatening salt wasting). “Nonclassic” is a late-onset form that presents with androgen excess, or it could be asymptomatic. Cannot convert 17-hydroxyprogesterone to 11-deoxycortisol → ↓ cortisol synthesis → ↑ adrenal stimulation → ↑ ACTH and androgens.
- **11β-Hydroxylase deficiency:** Second most common cause of adrenal hyperplasia. Cannot convert 11-deoxycortisol to cortisol or 11-deoxycorticosterone to corticosterone, also leading to ↑ ACTH and androgens.

History/PE

Androgen excess: Genital ambiguity, premature pubarche, menstrual irregularity, infertility, hirsutism, acne, and, rarely, a palpable abdominal mass.

Diagnosis

- Physical examination
- **21-Hydroxylase deficiency:** ↑17-OH progesterone levels (a substrate for 21-hydroxylase). This is part of the newborn screen. Cosyntropin (ACTH) stimulation test—gold standard but not necessary if ↑↑ 17-OH.
- **11β-Hydroxylase deficiency:** ↑ serum 11-deoxycortisol and 11-deoxycorticosterone.
- **Both:** Next, assessment of the following levels:
  - Cortisol → decreased.
  - Androstenedione → elevated in 21-hydroxylase and 11β-hydroxylase deficiency [right arrow] elevated. Also consider adrenal/ovarian neoplasm.
  - Dehydroepiandrosterone ([DHEA]) → elevated in 21-hydroxylase and 11β-hydroxylase deficiency [right arrow] elevated. Also consider adrenal neoplasm, Cushing syndrome.
- **If salt wasting:** Will also have ↓ aldosterone, ↓ sodium, ↑ potassium, and ↑ renin associated with hypovolemia.

KEY FACT

21-Hydroxylase deficiency can present with hypotension, whereas 11β-hydroxylase and 17-hydroxylase deficiencies can present with hypertension caused by accumulation of deoxycorticosterone.

Treatment

- Glucocorticoids (eg, dexamethasone). Medical therapy for adrenal and ovarian disorders prevents new terminal hair growth but does not resolve hirsutism.
- Addition of mineralocorticoid therapy (eg, fludrocortisone) if salt wasting or hypotension is present.
- Laser ablation, electrolysis, or conventional hair removal techniques for removal of unwanted hair.

POLYCYSTIC OVARIAN SYNDROME

A syndrome of excess testosterone and excess estrogen, PCOS has a prevalence of 6% to

10% among U.S. females of reproductive age and is the most common cause of infertility in females. Diagnosis requires fulfillment of two of the following three (Rotterdam criteria):

- Polycystic ovaries (via ultrasonography)
- Oligo-ovulation and/or anovulation
- Clinical and/or biochemical evidence of hyperandrogenism

MNEMONIC

The most severe form of PCOS is* HAIR-AN *syndrome:

Hyper**A**ndrogenism, **I**nsulin **R**esistance, and **A**canthosis **N***igricans.*

History/PE

- **Common presentation:** Obesity (body mass index [BMI] >30 kg/m^2), menstrual cycle disturbances, infertility, acne, androgenic alopecia, and hirsutism from hyperandrogenism
- **Females with PCOS also at ↑ risk for the following:**
    - **DM type 2:** Acanthosis nigricans possibly seen on examination
    - **Metabolic syndrome:** Insulin resistance, atherogenic dyslipidemia, and hypertension

Diagnosis

- **Biochemical testing of hyperandrogenemia:** ↑ testosterone
    - ↑ free testosterone more sensitive than total testosterone (total can be normal) because of low sex hormone–binding globulin
    - Excluding other causes of hyperandrogenism: DHEAS to rule out adrenal tumor
    - Pelvic ultrasound to rule out androgen-secreting ovarian tumor
    - 17-Hydroxyprogesterone to rule out nonclassical CAH
    - Screening in the setting of clinical signs of Cushing syndrome (eg, moon facies, buffalo hump, abdominal striae) or acromegaly (eg, ↑ head size)
- **Evaluation for metabolic abnormalities:**
    - Two-hour oral glucose tolerance test
    - Fasting lipid and lipoprotein levels (total cholesterol, HDL, LDL, triglycerides)
- **Optional tests:** Not necessary if both oligomenorrhea and signs of hyperandrogenism are present
    - **Transvaginal ultrasonography:** Look for more than 11 small (2–9 mm), subcapsular follicles forming a "pearl necklace" sign (see Fig. 2.11-7). Seen in roughly two thirds of females with PCOS.

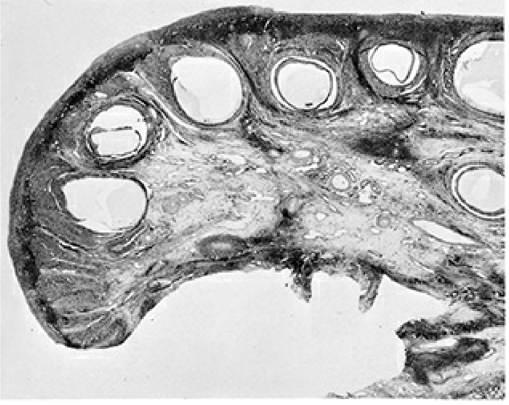


FIGURE 2.11-7. Polycystic ovary with prominent multiple cysts. (Reproduced with permission from DeCherney AH, Nathan R. *Current Diagnosis & Treatment: Obstetrics & Gynecology*, 10th ed. New York, NY: McGraw-Hill; 2007.)

  - **Gonadotropins:** ↑ LH/FSH ratio (>2:1)
  - **24-hour urine for free cortisol:** Adult-onset CAH or Cushing syndrome

Treatment

- **Females who are not attempting to conceive:** The physician can treat these patients with combined hormonal contraception or progestin ± an antiandrogen like spironolactone if there are symptoms of hyperandrogenism. Patients with metabolic syndrome or insulin resistance may benefit from the addition of metformin.
- **Females who are attempting to conceive:** Letrozole (aromatase inhibitor) ± metformin is first-line treatment for ovulatory stimulation. Clomiphene (selective estrogen receptor modulator) is second-line.
- **Symptom-specific treatment:**
  - **Hirsutism:** Combination OCPs first line; antiandrogens (spironolactone, finasteride) and metformin
  - **Obesity, cardiovascular risk factors, lipid levels:** Diet, weight loss (can also help regulate ovulation), and exercise plus potentially lipid-controlling medication (eg, statins)

KEY FACT

Combined hormonal contraception or progestin ↓ the risk for endometrial hyperplasia/carcinoma among women with PCOS.

Complications

- Infertility
- Miscarriage
- Type 2 DM
- Metabolic syndrome
- ↑ long-term risk for breast and endometrial cancers because of unopposed estrogen secretion

KEY FACT

Female causes of infertility are more common than male causes. An investigation should begin with history (including menstrual) and physical examination of the female and then progress to semen analysis before further workup in the female, as semen analysis is simple and noninvasive.

INFERTILITY

- Definition:
  - The inability to conceive after 12 months of regular, unprotected sexual intercourse in women <35 years of age

  - The inability to conceive after 6 months of regular, unprotected sexual intercourse in women ≥35 years of age
- Primary infertility characterized by no prior pregnancies; secondary infertility distinguished by at least one prior pregnancy. Etiologies are shown in Figure 2.11-8 and Table 2.11-8.

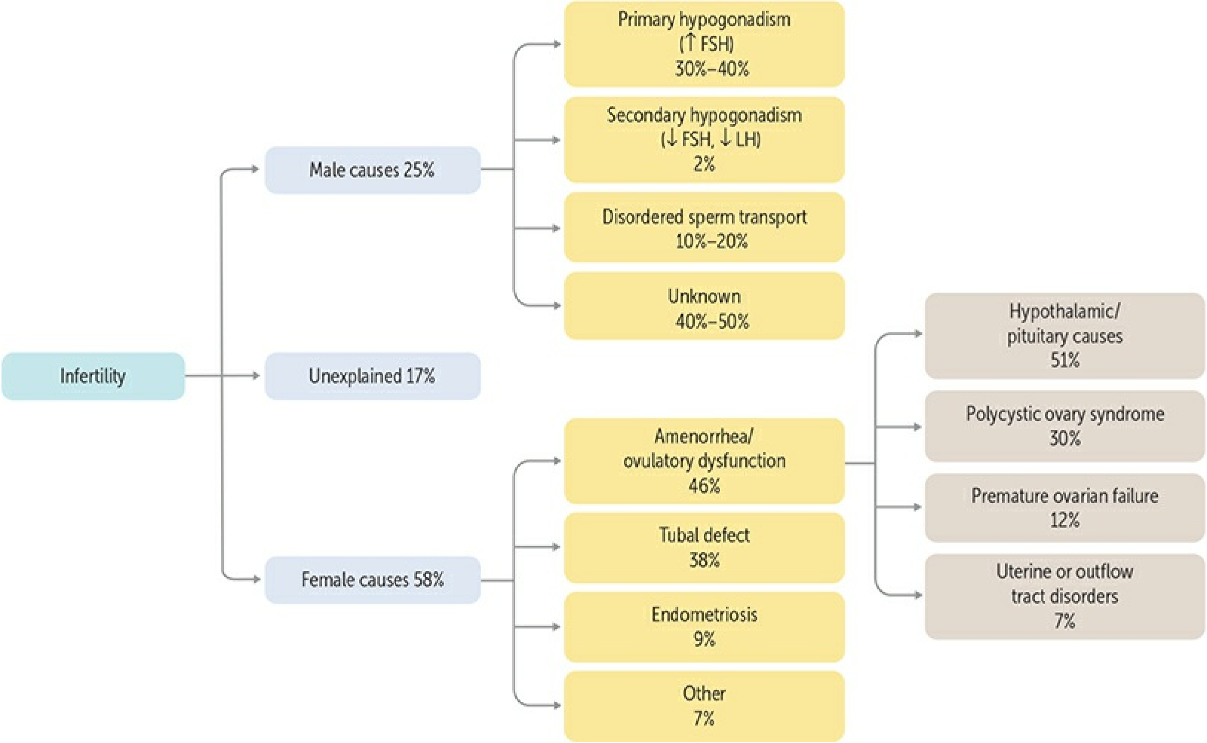

Infertility
Male causes 25%
Unexplained 17%
Female causes 58%
Primary hypogonadism (↑ FSH) 30%–40%
Secondary hypogonadism (↓ FSH, ↓ LH) 2%
Disordered sperm transport 10%–20%
Unknown 40%–50%
Amenorrhea/ ovulatory dysfunction 46%
Tubal defect 38%
Endometriosis 9%
Other 7%
Hypothalamic/ pituitary causes 51%
Polycystic ovary syndrome 30%
Premature ovarian failure 12%
Uterine or outflow tract disorders 7%

FIGURE 2.11-8. **Causes of infertility.** (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.11-8. **Infertility Workup**

ETIOLOGY	HISTORY/PE	DIAGNOSIS	TREATMENT
Male factors	Testicular injury or infection Medications (corticosteroids, cimetidine, spironolactone) Pituitary, thyroid, or liver disease Signs of hypogonadism Varicocele	Semen analysis TSH Prolactin Karyotyping (to rule out Klinefelter syndrome)	Treatment of hormonal deficiency Intrauterine insemination (IUI) Donor insemination In vitro fertilization (IVF) Intracytoplasmic sperm injection
Ovulatory factors	↑ incidence with age Symptoms of hyperthyroidism/hypothyroidism Galactorrhea Menstrual cycle abnormalities Pituitary tumors	Menstrual history Basal body temperature Ovulation predictor Midluteal progesterone Early follicular FSH ± estradiol level (ovarian reserve) TSH, prolactin, androgens Ovarian sonography (antral follicle count) Endometrial biopsy (luteal-phase defect)	Treatment depends on the etiology (eg, levothyroxine, dopamine) Induction of ovulation with clomiphene, gonadotropins IUI IVF
Tubal/pelvic factors	History of PID, appendicitis, endometriosis, pelvic adhesions, tubal surgery	Hysterosalpingogram Potential laparoscopy	Laparoscopic resection or ablation of endometriomas or fibroids IVF
Cervical factors	Cryotherapy, conization, or diethylstilbestrol (DES) exposure in utero	Physical exam	IUI IVF
Uterine factors	Polyps Fibroids Congenital anomalies	Ultrasound Hysterosalpingogram	Surgical treatment

MENOPAUSE

Cessation of menses for a minimum of 12 months as a result of follicular depletion.

History/PE

- The average age of onset is 51 years.
- Symptoms include hot flashes, pruritus, vaginal dryness caused by vaginal atrophy, insomnia, anxiety/irritability, poor concentration, mood changes, dyspareunia, and loss of libido.
- “Premature menopause” (also known as premature ovarian insufficiency) is cessation of menses before 40 years of age.

Diagnosis

A clinical diagnosis. The following studies are not routine but may be helpful:

- **Labs:** ↑ FSH
- Serum TSH should be measured because of overlap of symptoms and common age of presentation of hypothyroidism and menopause

Treatment

- **Best initial treatment:** HRT (combination estrogen and progestin) in symptomatic patients without contraindications <60:
  - Short-term use associated with a decrease in all-cause mortality. Risk:benefit ratio changes based on individual risk factors when considering continuing therapy long-

term

  - May ↑ the incidence of breast cancer with long-term use at high doses
  - May ↑ cardiovascular mortality if initiated at age >60 and/or greater than 10 years from the menopausal transition
  - **Contraindications:** Vaginal bleeding, breast cancer (known or suspected), untreated endometrial cancer, history of thromboembolism, chronic liver disease, hypertriglyceridemia, known coronary artery disease
- **Non-HRT (for those with contraindications to HRT listed earlier):** Selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs), clonidine, and/or gabapentin to ↓ the frequency of hot flashes
- **Topical estrogen preparation:** Useful for vaginal atrophy; topical estrogen preparation does NOT have the same contraindications as systemic HRT
- **Calcium supplements ± bisphosphonates:** Useful for osteoporosis; dual-energy x-ray absorptiometry (DEXA) scan is used to measure bone mineral density (BMD); supplemental treatment includes daily calcium/vitamin D and weight-bearing exercise

KEY FACT

Postmenopausal women should be routinely screened for osteoporosis, starting at 65 years of age or earlier if there are additional risk factors.

GYNECOLOGIC DISORDERS

CYST AND ABSCESS OF THE BARTHOLIN DUCT

Obstruction of the Bartholin duct may lead to cyst formation, as mucus continues to accumulate behind the obstruction, causing cystic dilation. An obstructed Bartholin duct that becomes infected can develop a polymicrobial abscess.

History/PE

- **Cysts:** 1 to 3 cm in size, unilateral, and often asymptomatic. Larger cysts lead to periodic, painful swelling and dyspareunia.
- **Clinical diagnosis:** Mass at medial labia majora or lower vestibular area on physical examination.
- **Abscess:** Extremely painful, warm, fluctuant mass at medial labia majora or lower vestibule with possible cellulitis and fever.

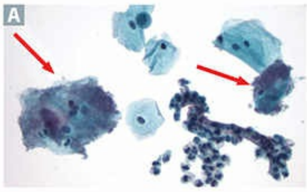
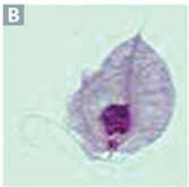
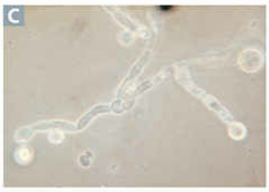
Treatment

- **Asymptomatic cysts:** No therapy ± warm soaks. The physician can consider drainage and biopsy if patient >40 years of age to exclude carcinoma.
- **Abscess:** Aspiration or incision and drainage to prevent reaccumulation. The physician should order tests for gonorrhea and chlamydia and other pathogens.
- Antibiotics are unnecessary unless cellulitis or sexually transmitted infection (STI) is present.

VAGINITIS

A spectrum of conditions that cause vulvovaginal symptoms such as itching, burning, irritation, and abnormal discharge. The most common causes are bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis (see Table 2.11-9).

TABLE 2.11-9. Causes of Vaginitis

VARIABLE	BACTERIAL VAGINOSIS	TRICHOMONIASIS	CANDIDIASIS
Incidence	15%–50% (most common)	5%–50%	15%–30%
Etiology	Not an infection: shift in vaginal flora (↑ anaerobes such as *Gardnerella vaginalis*, ↓ lactobacilli)	Protozoal flagellates (an STD)	Usually *Candida albicans*
Risk factors	Pregnancy, multiple sexual partners, female sexual partner, frequent douching	Unprotected sex with multiple partners	DM, antibiotic use, pregnancy, corticosteroids, HIV, OCP use, frequent intercourse, tight-fitting clothing
History	"Fishy" odor, thin homogenous white or gray discharge	↑ yellow-green discharge, odor, pruritus, dysuria	Pruritus, dysuria, burning, cottage cheese discharge
Examination	Mild vulvar irritation, thin homogenous white or gray discharge; pH >4.5	"Strawberry petechiae" in the upper vagina/cervix; pH >4.5	Erythematous, excoriated vulva/vagina with cottage cheese discharge; pH <4.5 (normal)
Discharge	Homogeneous, grayish-white with "fishy"/stale odor	Profuse, malodorous, yellow-green, frothy	Thick, white, curdy texture without odor
Wet mount	"Clue cells" (epithelial cells coated with bacteria [see red arrows in Image A])	Motile trichomonads (flagellated organisms slightly larger than WBCs [see Image B])	Budding yeast or hyphae
KOH prep	⊕ "Whiff" test ("fishy" odor)	N/A	Pseudohyphae (see Image C)
Treatment	Oral (PO) or vaginal metronidazole or vaginal clindamycin	Single-dose PO metronidazole or tinidazole for both partners Treatment of partners; otherwise, a "ping-pong effect"	Topical azole or PO fluconazole
Complications	Chorioamnionitis/endometritis, infection, preterm delivery, PID 	Same as for bacterial vaginosis 	

History/PE

- Presents with a change in discharge, malodor, pruritus, irritation, burning, swelling, dyspareunia, and dysuria
- Normal secretions as follows:
  - Midcycle estrogen surge: Clear, elastic, mucoid secretions
  - Luteal phase/pregnancy: Thick and white secretions that adhere to the vaginal wall
- A thorough examination of the vulva, vaginal walls, and cervix
- Many WBCs and no organism on saline smear—suspect *Chlamydia trachomatis*, an intracellular organism

Q

A 56-year-old woman presents with presents with insomnia, vaginal dryness, and lack of menses for 13 months. What is the most likely diagnosis?

A

The most likely diagnosis is menopause. Menopause is a clinical diagnosis determined retrospectively after 12 months of amenorrhea without any other obvious physiologic or pathologic cause. However, a physician trying to rule out menopause as a cause of secondary amenorrhea may consider ordering an FSH level. Elevation is suggestive of menopause.

Diagnosis/Treatment

- Vaginal fluid for vaginal pH, amine ("whiff") test, wet mount (with saline), and 10% potassium hydroxide (KOH) microscopy (Fig. 2.11-9).

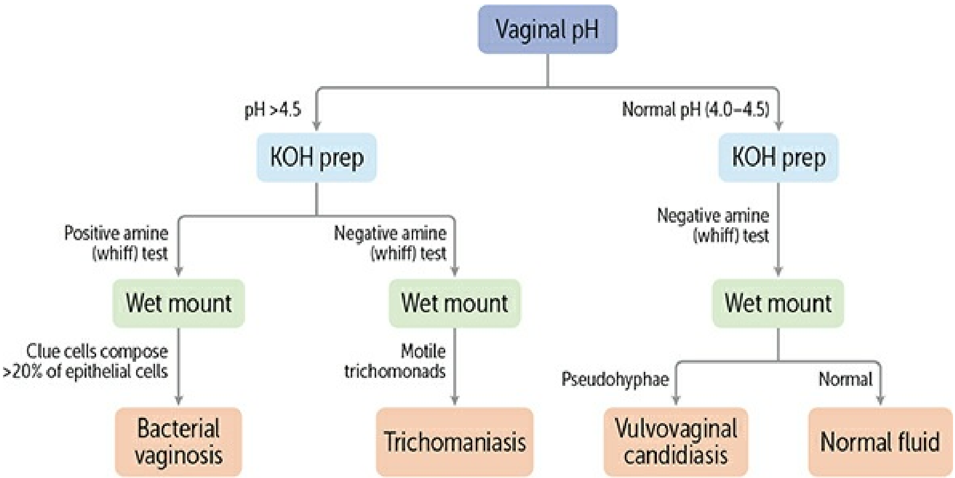

Vaginal pH
pH >4.5
Normal pH (4.0–4.5)
KOH prep
KOH prep
Positive amine (whiff) test
Negative amine (whiff) test
Negative amine (whiff) test
Wet mount
Wet mount
Wet mount
Clue cells compose >20% of epithelial cells
Motile trichomonads
Pseudohyphae
Normal
Bacterial vaginosis
Trichomaniasis
Vulvovaginal candidiasis
Normal fluid

FIGURE 2.11-9. **Using vaginal pH and wet mount to diagnose common vaginal infections.** (Reproduced with permission from USMLE-Rx.com.)

- If purulent discharge, numerous leukocytes on wet prep, cervical friability, and any symptoms of PID: Nucleic acid amplification testing (NAAT) or cultures for *Neisseria gonorrhoeae* or *C trachomatis* to rule out cervicitis. NAAT is the gold-standard test.
- Treatment: Etiology specific (see Table 2.11-9).

KEY FACT

Criteria for the clinical diagnosis of bacterial vaginosis (three of four are required):

- Abnormal whitish-gray discharge
- Vaginal pH >4.5
- ⊕ amine ("whiff") test
- Clue cells composing >20% of epithelial cells on wet mount

CERVICITIS

Inflammation of the uterine cervix. Etiologies are as follows:

- **Infectious (most common):**
    - *C trachomatis* and *N gonorrhoeae* are most common.
    - *C trachomatis* is more common than *N gonorrhoeae* in mucopurulent cervicitis.
    - *Trichomonas* and herpes simplex virus (HSV) are less common causes of cervicitis.
- **Noninfectious:** Trauma, radiation exposure, malignancy
- All sexually active women <25 years of age should undergo yearly screening for *C trachomatis* and *N gonorrhoeae* because of increased rates of asymptomatic infection and increased risk for infertility in untreated infections.

History/PE

Mucopurulent discharge; ⊕ cervical motion tenderness; absence of other signs of PID

Diagnosis and Treatment

Relevant discussion of STIs in the Renal/Genitourinary chapter. If mucopurulent discharge is present, empiric treatment for both *C trachomatis* and *N gonorrhoeae* is warranted.

KEY FACT

Genital ulcers:

- *Treponema pallidum* causes single **painless** chancres.
- *Haemophilus ducreyi* (doo·**kray**·ee) causes **deep** painful ulcers with irregular borders (you "do cry").
- HSV causes multiple **shallow** painful ulcers.

PELVIC INFLAMMATORY DISEASE

PID is a polymicrobial infection of the upper genital tract associated with *N gonorrhoeae* (one third of cases), *C trachomatis* (one third of cases), and endogenous aerobes/anaerobes. Risk factors include uterine instrumentation or procedure, douching, smoking, multiple sex partners, and prior STDs and/or PID. Most cases are not secondary to STDs.

Q 1

A 20-year-old woman is diagnosed with trichomoniasis and prescribed an antibiotic. She calls her physician, reporting of flushing, nausea, and emesis. What antibiotic was the patient prescribed, and what should she have been warned of?

Q 2

A 23-year-old woman presents with fever and abdominal pain of 2 days' duration. She has a ⊕ cervical motion tenderness. Antibiotics are started. What is the next step in management?

History/PE

- Presents with lower abdominal pain, fever, chills, menstrual disturbances, and purulent cervical discharge

- Cervical motion tenderness and adnexal tenderness
- Orogenital contact that can cause gonococcal pharyngitis along with PID

Diagnosis

- Diagnosed by the presence of acute lower abdominal or pelvic pain plus one of the following:
  - Uterine tenderness
  - Adnexal tenderness
  - Cervical motion tenderness
- First, a β-hCG test to rule out pregnancy
- **Best test:** NAAT for *N gonorrhoeae* and *C trachomatis*
- A WBC count >10,000 cells/μL: Poor positive and negative predictive values for PID
- Ultrasonography (not sensitive or specific): Possibly showing thickening or dilation of the fallopian tubes, fluid in the cul-de-sac, a multicystic ovary, or tubo-ovarian abscess

MNEMONIC

Acute causes of pelvic pain—

A ROPE

Appendicitis—Periumbilical → right lower quadrant (RLQ) pain, fever, nausea, vomiting
Ruptured ovarian cyst—Recent strenuous physical activity
Ovarian torsion or abscess—Torsion: severe unilateral pain (may be colicky), nausea, vomiting; abscess: gradual onset of fever, vaginal discharge, respectively
PID—Gradual onset of fever, vaginal discharge
Ectopic pregnancy—To be ruled out with β-hCG test

Treatment

- Antibiotic treatment should not be delayed while awaiting culture results. All sexual partners should be examined and treated appropriately.
- **Outpatient regimens:**
  - **Regimen A:** Ceftriaxone IM for one dose + doxycycline PO for 14 days ± metronidazole PO for 14 days (metronidazole covers anaerobic infections).
  - **Regimen B:** Ofloxacin or levofloxacin for 14 days ± metronidazole for 14 days. This is only in special cases because there is an increase in quinolone-resistant *N gonorrhoeae.*
  - Treatment should not be delayed for NAAT.
- **Inpatient antibiotic regimens:**
  - Cefoxitin or cefotetan plus doxycycline for 14 days
  - Clindamycin plus gentamicin for 14 days
- **Additional intervention:**
  - Drainage of a tubo-ovarian/pelvic abscess is appropriate if mass persists after antibiotic treatment, abscess is >4 to 6 cm, or mass is in the cul-de-sac in the midline and drainable through the vagina.
- If the patient's condition deteriorates, the case calls for exploratory laparoscopy or laparotomy.
- Surgery may range from total hysterectomy and bilateral oophorectomy with lysis of

adhesions in severe cases to conservative surgery for females who desire to maintain fertility.

KEY FACT

Mild and subclinical PID are major causes of tubal factor infertility, ectopic pregnancy, and chronic pelvic pain caused by pelvic scarring.

Complications

- Repeated episodes of infection, chronic pelvic pain, dyspareunia, and ectopic pregnancy
- Infertility (10% after the first episode, 25% after the second episode, and 50% after a third episode)
- Fitz-Hugh–Curtis syndrome (presents with associated perihepatitis, right upper quadrant [RUQ] pain, abnormal liver function, and referred right shoulder pain)

1 A

She was prescribed metronidazole. She should have been warned to abstain from alcohol while taking it, as metronidazole causes a disulfiramlike reaction.

2 A

The next step in management is pelvic ultrasonography to rule out tubo-ovarian abscess.

OVARIAN TORSION

Twisting of the ovarian vascular pedicle that occludes venous and/or arterial flow to the ovary, leading to ischemia.

History/PE

- Colicky, lower quadrant abdominal pain of acute onset with peritoneal signs, nausea, and vomiting.
- Risk factors, including PCOS and ovarian tumors and cysts.
- Most common times for torsion in pregnancy: 18 weeks' gestation, when the uterus is rising over the pelvic brim or immediately postpartum with uterine involution. The increased motion of the uterus at these times increases the risk for torsion.

Diagnosis

Best initial test:

- Ultrasound with Doppler may show ovarian abnormal venous or arterial flow.
- CT can help with visualization of an ovarian mass or cyst but will not provide information on blood flow to the ovary.
- False negatives are possible due to intermittent torsion. If suspicion persists following a negative ultrasound, surgical evaluation is indicated.

Treatment

Laparoscopy or laparotomy with detorsion if the ovary is still viable or oophorectomy if not viable

PEDIATRIC VAGINAL DISCHARGE

Etiologies of vaginal discharge in pediatric patients include the following:

- **Foreign objects:** Most common cause of vaginal discharge in pediatric patients
- **Infectious vulvovaginitis:** May present with a malodorous, yellow-green, purulent discharge. Causes include the following:
    - **Group A *Streptococcus*:** The most common infectious cause
    - ***Candida*:** Recent antibiotic therapy, immunosuppression (eg, diabetes); rare in children
    - **STIs:** Typically from sexual abuse
- **Noninfectious vulvovaginitis:** Potential causes include poor hygiene, contact dermatitis, and eczema
- **Sarcoma botryoides (rhabdomyosarcoma):** A malignancy with lesions that have the appearance of "bunches of grapes" within the vagina

KEY FACT

Pediatric vaginal discharge may be normal, but STDs resulting from sexual abuse must be ruled out and, if found, reported to Child Protective Services.

TOXIC SHOCK SYNDROME

Caused by a reaction to toxic shock syndrome toxin 1 (TSST-1), a preformed *Staphylococcus aureus* toxin. Menstrual cases occur due to retained tampons (used for longer than recommended). Nonmenstrual cases are nearly as common as menstrual cases and occur in the setting of surgical wounds and burns.

History/PE

- Presents with abrupt onset of fever, vomiting, and watery diarrhea
- A diffuse macular erythematous rash involving the palms and soles
- Nonpurulent conjunctivitis common
- Desquamation, especially of the palms and soles, generally occurring during recovery within 1 to 2 weeks of illness

KEY FACT

Toxic shock syndrome (TSS) is a rare but potentially fatal reaction to *S aureus* toxin, not to the bacterium itself.

Diagnosis

- Based on clinical presentation: Fever >102°F (38.9°C), hypotension, skin findings, involvement of three or more organ systems

- ⊖ blood cultures, given that TSS is caused by a preformed toxin and not invasive properties of the organism

Treatment

- Rapid rehydration, examination for foreign objects in vaginal canal, drainage if localized infection found
- Empiric antibiotics: Clindamycin + vancomycin; clindamycin is used for its antitoxin properties
- If methicillin-sensitive *S aureus* isolated in wound, clindamycin + oxacillin OR nafcillin
- If methicillin-resistant *S aureus* isolated, clindamycin + vancomycin OR linezolid

Complications

- Mortality rate associated with TSS is 3% to 6%.
- Causes of death include cardiac arrhythmias, cardiomyopathy, respiratory failure caused by acute respiratory distress syndrome (ARDS), and coagulopathy caused by disseminated intravascular coagulation (DIC).

BENIGN BREAST DISORDERS

NONPROLIFERATIVE BREAST LESIONS

Generally, no increased risk for breast cancer. Simple breast cysts are the most common; they are fluid-filled masses stemming from an exaggerated stromal tissue response to hormones and growth factors.

- **Fat necrosis of the breast:**
  - Benign condition that presents radiographically like breast cancer, but the breast biopsy reveals fat globules. No further workup indicated.
  - Secondary to trauma to the breast or caffeine use.
  - Typically, females 30 to 50 years of age develop nonproliferative breast lesions (postmenopausal females rarely develop them).
  - Provide reassurance and pain control.
- **Fibrocystic changes of the breast:**
  - Benign condition that presents as bilateral breast tenderness with diffuse, cordlike thickening of the breasts with no discharge
  - Tenderness worsens during menstruation
- **Fibroadenoma:**
  - Benign condition that presents as solitary, mobile, well-circumscribed nodule
  - Tenderness and size increase during menstruation
  - Classically seen in women <30 years of age
  - Provide reassurance and pain control
  - Discussed more later

KEY FACT

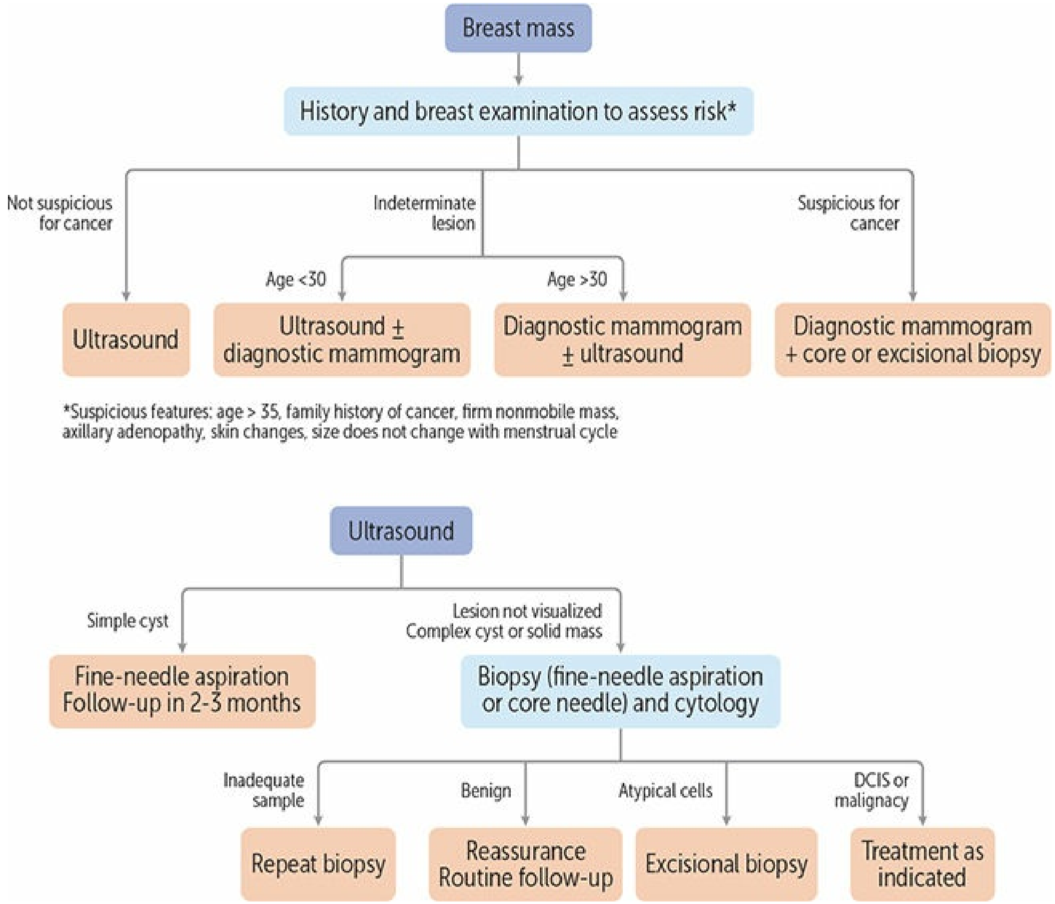
The differential diagnosis of a breast mass includes fibrocystic disease, breast cyst fibroadenoma, mastitis/abscess, fat necrosis, and breast cancer.

History/PE

- Cyclic bilateral mastalgia and swelling, most prominent just before menstruation
- Rapid fluctuation in size of masses—a common finding

Diagnosis

- See Figure 2.11-10 for an algorithm of a breast mass workup.



Breast mass
History and breast examination to assess risk*
Not suspicious for cancer
Indeterminate lesion
Suspicious for cancer
Age <30
Age >30
Ultrasound
Ultrasound ± diagnostic mammogram
Diagnostic mammogram ± ultrasound
Diagnostic mammogram + core or excisional biopsy
*Suspicious features: age > 35, family history of cancer, firm nonmobile mass, axillary adenopathy, skin changes, size does not change with menstrual cycle
Ultrasound
Simple cyst
Lesion not visualized
Complex cyst or solid mass
Fine-needle aspiration
Follow-up in 2-3 months
Biopsy (fine-needle aspiration or core needle) and cytology
Inadequate sample
Benign
Atypical cells
DCIS or malignancy
Repeat biopsy
Reassurance
Routine follow-up
Excisional biopsy
Treatment as indicated

FIGURE 2.11-10. Workup of a breast mass. (Reproduced with permission from USMLE-Rx.com.)

- First, have patient return after menstruation, because symptoms fluctuate with hormones.
- **Best initial test:** If unchanged on follow-up, perform ultrasonography to differentiate a mass from a fluid-filled one vs a solid one.
- **Subsequent test:** Fine-needle aspiration (FNA) of a discrete mass that is suggestive of a cyst is indicated to alleviate pain and to confirm the cystic nature of the mass.
- **Most accurate test:** Excisional biopsy is indicated if no fluid is obtained or if the fluid is bloody on aspiration.
- Mammography is of limited use (especially if <35 years of age because of density of breast tissue).
- There is no ↑ risk for breast cancer if patient has a simple cyst, but there is ↑ risk if patient has a complex cyst (ductal epithelial hyperplasia or cellular atypia), which is rare.

KEY FACT

Intraductal papilloma and mammary duct ectasia are common causes of bloody nipple discharge.

PROLIFERATIVE BREAST LESIONS WITHOUT ATYPIA

Include intraductal papillomas, sclerosing adenosis, and usual ductal hyperplasia. Associated with a small increased risk for breast cancer. An intraductal papilloma is composed of papillary cells growing from the wall of a cyst into the lumen.

- ***Dx:*** These lesions are diagnosed with core needle biopsy. Surgical excision is required to exclude atypia or ductal carcinoma in situ (DCIS).
- ***Tx:*** Sclerosing adenosis and usual ductal hyperplasia require no treatment.

Q 1

A 30-year-old woman was in a car accident 1 week ago and subsequently notices a hardened bump in the left breast. What is this likely to be, and what can be found on biopsy?

Q 2

A 27-year-old woman palpates a 1 cm × 1 cm new breast mass on self-examination. What is the first step in the workup of the mass?

INTRADUCTAL PAPILLOMA

Papillary tumor affecting a single lactiferous duct. It is the most common cause of blood discharge in middle-aged women.

- ***Hx/PE:*** Presents as unilateral bloody discharge from nipple in 40- to 50-year-old females.
- ***Dx:*** Obtain breast ultrasound or mammography (decision based on age of patient). Obtain a needle biopsy or FNA.
- ***Tx:*** Excision is curative.

PHYLLODES TUMOR

Can sometimes be difficult to distinguish from a fibroadenoma. It is generally larger with greater metastatic ability, and the differentiating features are the papillary projections of the stroma, lined with epithelium and associated with hyperplasia and atypia. Phyllodes tumors should be completely excised; axillary lymph node dissection is not necessary (see Fig. 2.11-11).

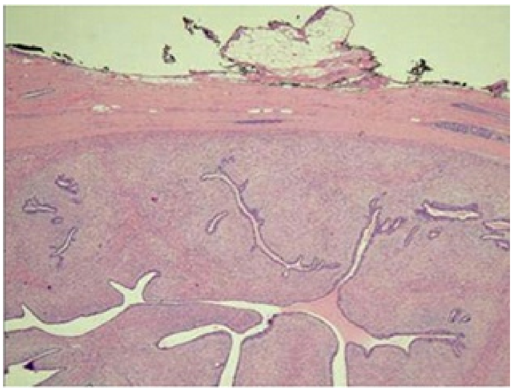


FIGURE 2.11-11. **Phyllodes tumor with classic "leaflike" appearance.** (Reproduced with permission from Crenshaw SA et al. Immediate breast reconstruction with a saline implant and AlloDerm, following removal of a Phyllodes tumor. *World J Surg Oncol.* 2011;9:34.)

ATYPICAL HYPERPLASIA

Atypical hyperplasia (AH) can be ductal or lobular, filling part of but not the entire duct or lobule.

- Similar to a low-grade DCIS or lobular carcinoma in situ (LCIS) with a moderately increased risk for breast cancer
- Found incidentally in biopsy done after a suspicious mammogram
- Requires risk reduction, which involves yearly mammograms and tamoxifen or aromatase inhibitor (if postmenopausal)

BREAST CANCER

The most common cancer (affects one in eight women) and the second most common cause of cancer death in females (after lung cancer) in the United States. Sixty percent occur in the upper outer quadrant. One half of newly diagnosed patients have risk factors. Risk factors include the following:

- Female sex; older age (above 40 years of age)
- A personal history of breast cancer; family history in a first-degree relative; genetic factors (*BRCA1* and *BRCA2* mutations: associated with early onset)
- Alcohol; cigarettes (controversial)
- Exposure to radiation
- A history of fibrocystic change with cellular atypia
- ↑ exposure to estrogen (nulliparity, early menarche, late menopause, first full-term pregnancy after 35 years of age, PCOS, HRT)

History/PE

Clinical manifestations include the following:

- **Early findings:** Single, nontender, immovable, firm-to-hard mass with ill-defined margins or mammographic abnormalities on routine screening
- **Later findings/locally advanced:**
  - Axillary lymphadenopathy, breast enlargement, pain, peau d'orange skin findings suggesting inflammation (redness, thickening, dimpling), fixation of the mass to the

skin or chest wall
    - Prolonged unilateral scaling erosion (with eczematous rash) of the nipple that spreads to the areola with or without discharge (Paget disease of the nipple, specific for DCIS)
- **Late findings:** Ulceration, supraclavicular lymphadenopathy, edema of the arm
- **Metastatic disease:**
    - Metastases to the bone (pain), lung (dyspnea, cough), and liver (abdominal pain, nausea, jaundice)
    - A firm or hard axillary node >1 cm
    - Axillary nodes that are matted or fixed to the skin (stage III); ipsilateral supraclavicular or infraclavicular nodes (stage IV)

MNEMONIC

Common metastases to bone—

BLT and Kosher Pickle on top

Breast
Lung
Thyroid
Kidney
Prostate

KEY FACT

Hormone-containing contraception is contraindicated in patients with breast cancer. The safest option for contraception is a copper IUD.

1 A

This is fat necrosis of the breast. This commonly occurs after trauma that is not always remembered. It is a mimicker of breast cancer in terms of presentation and radiographic findings. Biopsy results differentiate the two and reveal coarse (not micro) calcifications and foamy macrophages.

2 A

Ultrasonography. The patient is <30 years of age, so ultrasonography is the preferred means of distinguishing a solid mass from a cyst.

Diagnosis

Majority of breast cancers diagnosed from mammography.

- **Screening:**
    - **Postmenopausal women:** Mammography. The physician should look for ↑ density with microcalcifications, irregular borders, and spiculated mass. Mammography can

detect lesions roughly 2 years before they become clinically palpable (see Fig. 2.11-14A).

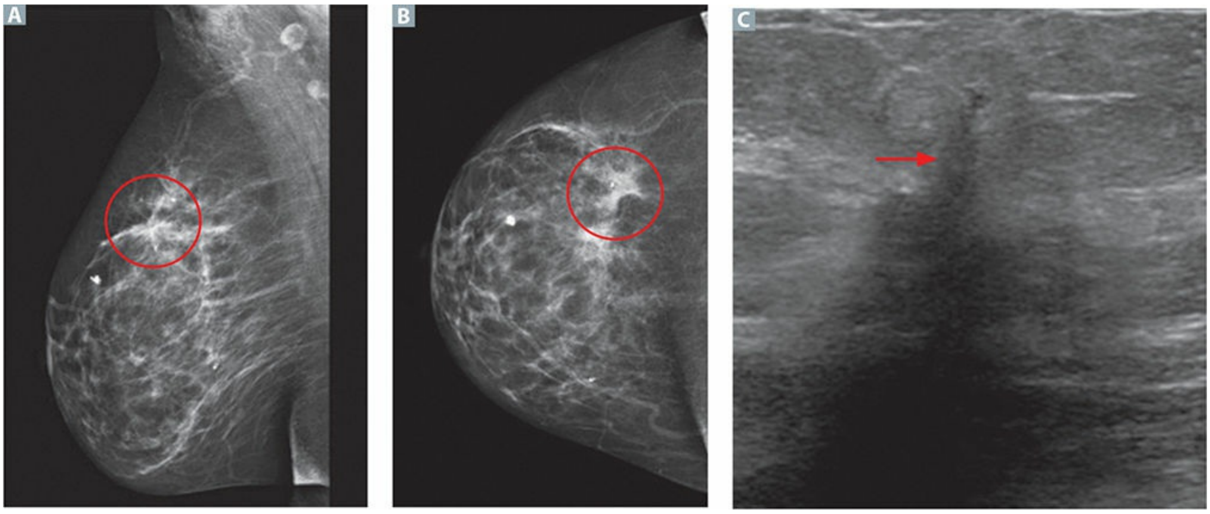


FIGURE 2.11-12. **Breast cancer.** Mediolateral oblique **(A)** and craniocaudal **(B)** views from a mammogram demonstrate a spiculated mass with a satellite mass (*circles in A and B)* in the central and outer upper right breast. A targeted breast ultrasonogram **(C)** in a different patient demonstrates a hypoechoic mass (*arrow)* that is taller than it is wide and exhibits dense posterior acoustic shadowing. (Reproduced with permission from USMLE-Rx.com.)

  - **Premenopausal women:** Ultrasonography for females <30 years of age because of density of breast tissue; can distinguish a solid mass from a benign cyst (see Fig. 2.11-14C).
- Women with the following risk factors are recommended by the American Cancer Society to undergo annual MRI screening:
  - Known *BRCA* mutation
  - First-degree relative who is a *BRCA* carrier
  - Lifetime risk for breast cancer that is 20% to 25% or greater
- **Biopsy of suspicious lesions on mammography:**
  - A mammography-guided FNA or core needle biopsy. A full-thickness skin biopsy should be done if signs of inflammation are present.
  - **FNA:** A good initial biopsy, especially for lesions close to the skin; however, it is a small sample with a high false-⊖ rate. FNA may also be used to follow response to treatment.
  - **Core needle biopsy:** A larger sample that allows testing for receptor status.
  - **Open biopsy:** Less commonly used. It provides tissue for a more accurate diagnosis and allows immediate resection of tumor; however, an open biopsy requires taking the patient to the operating room.

KEY FACT

The first step in the workup of a suspicious mass in postmenopausal females and in those >30 years of age is a mammogram. For premenopausal females <30 years of age, the first step should be an ultrasound.

- **Receptor status of tumor:** Determination of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) status

- **Tumor markers for recurrent breast cancer:** Typically used for metastatic disease as a proxy to monitor treatment response. Include carcinoembryonic antigen (CEA) and cancer antigen (CA) 15-3 or CA 27-29.
- **Metastatic disease:**
  - **Imaging:** X-ray of the chest (CXR); CT of the chest, abdomen, and pelvis; brain MRI. Positron emission tomography (PET) and bone scans can also be useful.

Treatment

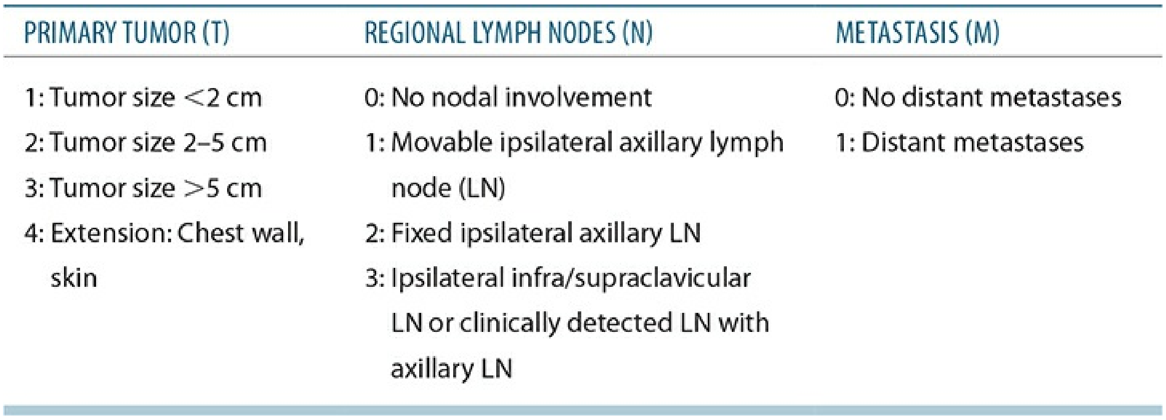
- **Early stage:**
  - Breast-conserving surgery + radiation or mastectomy ± radiation (if cancer in deep margins or axillary lymph nodes). In both cases, the situation also calls for sentinel node biopsy for evaluation of axillary lymph nodes.
  - Adjuvant therapy as indicated.
- **Locally advanced:**
  - Neoadjuvant chemotherapy + HER2-directed therapy to reduce size of tumor to allow for breast-conserving therapy as opposed to mastectomy
  - Breast conservation surgery or mastectomy with sentinel lymph node biopsy
  - Adjuvant therapy as indicated
- **Adjuvant therapy:**
  - All ER/PR ⊕ patients should receive tamoxifen (a selective estrogen receptor modulator [SERM] that competitively antagonizes the ER, inhibiting the growth of breast cancer cells) or an aromatase inhibitor if postmenopausal (inactivates aromatase that converts peripheral androgens to estrogens).

KEY FACT

In a postmenopausal woman with a new breast lesion, the physician should maintain a high degree of clinical suspicion for breast cancer.

-
  - All HER2⊕ patients should receive HER2-directed therapies such as trastuzumab, a monoclonal antibody that binds to HER2 receptors on the cancer cell (watch for cardiotoxicity).
  - ER, PR, and HER2⊖ patients should receive chemotherapy if tumor >0.5 cm.
- **Contraindications to breast-conserving therapy (lumpectomy):** Large tumor size, subareolar location, multifocal tumors, fixation to the chest wall, prior radiation to the chest wall, or involvement of the nipple or overlying skin.
- **Stage IV disease:** Treated with radiation therapy, hormonal therapy, and biologic therapy (depending on the receptor status of the tumor).
- Table 2.11-10 describes the breast cancer stages.

TABLE 2.11-10. Breast Cancer Stages



PRIMARY TUMOR (T)	REGIONAL LYMPH NODES (N)	METASTASIS (M)
1: Tumor size <2 cm	0: No nodal involvement	0: No distant metastases
2: Tumor size 2–5 cm	1: Movable ipsilateral axillary lymph node (LN)	1: Distant metastases
3: Tumor size >5 cm	2: Fixed ipsilateral axillary LN	
4: Extension: Chest wall, skin	3: Ipsilateral infra/supraclavicular LN or clinically detected LN with axillary LN	

KEY FACT

Tamoxifen use is associated with hot flashes, endometrial cancer, and venous thromboembolism because it has mixed antagonist (breast) and agonist (endometrium) activity on estrogen receptors.

KEY FACT

Stage II of breast cancer is associated with tumor size >2 cm, stage III is associated with nodal involvement, and stage IV is associated with metastases.

Prognosis

- TNM staging (I–IV) is the most reliable indicator of prognosis.
- ⊕ ER status and PR status are associated with a favorable prognosis.
- Cancer localized to the breast has a 75% to 90% cure rate. With spread to the axilla, the 5-year survival rate is 40% to 50%.

Complications

Pleural effusion is common in patients with metastatic breast cancer; edema of the arm is common secondary to nodal involvement.

KEY FACT

Inflammatory breast carcinoma is rare, but it is an aggressive cancer that presents with peau d'orange skin (edematous cutaneous thickening) along with a red and painful breast mass. Axillary lymphadenopathy is typically present.

BENIGN GYNECOLOGIC DISORDERS

UTERINE LEIOMYOMAS (FIBROIDS)

Fibroids are the most common benign neoplams of the female genital tract. They present as singular or multiple discrete, round, and firm tumors. Composed of smooth muscle and connective tissue, fibroids may cause infertility or menorrhagia.

- Fibroids are hormone sensitive; size will ↑ in pregnancy and ↓ after menopause.
- Malignant transformation to leiomyosarcoma is rare (0.1%–0.5%).
- **Prevalence:** More common in Black females (50%) than in White females (25%)

KEY FACT

An irregular and mobile uterus is the key physical examination finding for fibroids.

History/PE

- Majority of cases are asymptomatic.
- Symptomatic patients may present with the following:
  - **Bleeding:** Longer, heavier periods; anemia
  - **Mass effect:** Pelvic/rectal pressure, constipation, and urinary frequency or retention
  - **Pain:** Secondary dysmenorrhea, dyspareunia
  - **Pelvic symptoms:** A firm, nontender, irregular, enlarged (“lumpy-bumpy”), or cobblestone uterus may be felt on physical examination.

KEY FACT

If a uterine mass continues to grow after menopause, suspect malignancy.

Diagnosis

- **Physical examination**
- **Ultrasonography (transvaginal):** To look for uterine myomas; can also exclude ovarian masses. Calcification indicates necrosis.
- **MRI:** Can delineate intramural, subserosal, and submucous myomas. The best modality for visualization, MRI is usually reserved in preparation for surgery or if there is concern for leiomyosarcoma (a new or growing mass in a postmenopausal female).
- **CBC:** To assess for anemia.

Treatment

- If asymptomatic, expectant management with annual pelvic exams and CBCs as needed
- **Pharmacologic:**
  - Combined hormonal contraception
  - Medroxyprogesterone acetate or danazol to slow or stop bleeding
  - GnRH analogues (leuprolide or nafarelin) to ↓ the size of myomas, suppress further growth, and ↓ surrounding vascularity. These also may be used before surgery to decrease uterine size, help with anemia, and allow a minimally invasive approach to hysterectomy.
  - NSAIDs for pain.
- **Surgery:**
  - **Females of childbearing years:** Abdominal or hysteroscopic myomectomy
  - **Females who have completed childbearing:** Hysterectomy.
  - **Uterine artery embolization** (~25% will need further invasive treatment)

- Emergent surgery may be required if torsion of a pedunculated myoma occurs

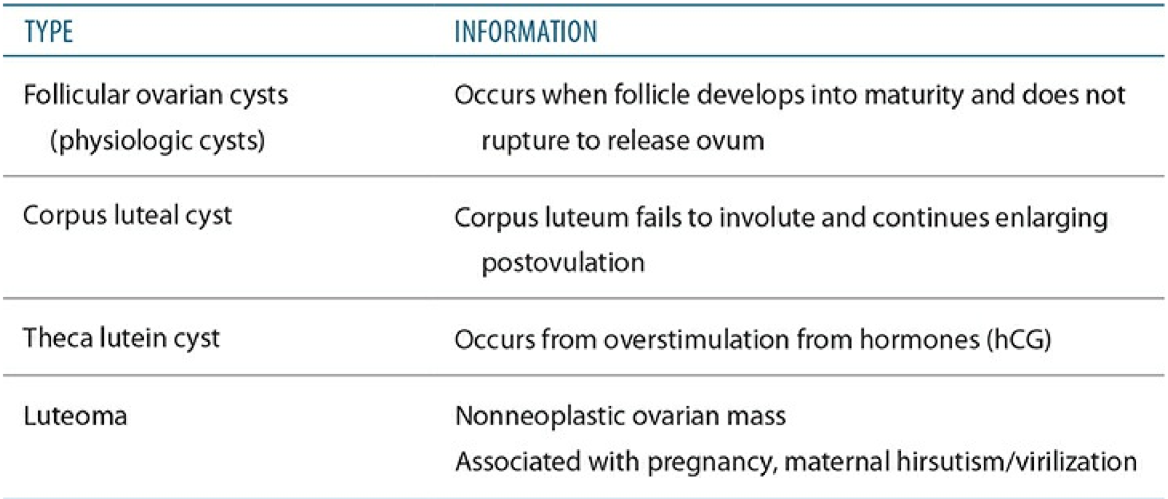
Complications

Infertility may be caused by a myoma that distorts the uterine cavity and plays a role similar to that of an IUD.

NONNEOPLASTIC OVARIAN CYSTS

Nonneoplastic cysts are the most common cause of ovarian enlargement (see Table 2.11-11). Ovarian lesions are more likely to be benign if unilateral, simple, smaller than 8 cm, and in women <45 years of age. Malignant ovarian lesions are discussed in detail later in this chapter.

TABLE 2.11-11. Common Benign Ovarian Cysts (Nonneoplastic)



TYPE	INFORMATION
Follicular ovarian cysts (physiologic cysts)	Occurs when follicle develops into maturity and does not rupture to release ovum
Corpus luteal cyst	Corpus luteum fails to involute and continues enlarging postovulation
Theca lutein cyst	Occurs from overstimulation from hormones (hCG)
Luteoma	Nonneoplastic ovarian mass Associated with pregnancy, maternal hirsutism/virilization

GYNECOLOGIC NEOPLASMS

Gynecologic cancers include uterine, endometrial, ovarian, cervical, and vulvar neoplasms. Ovarian cancer carries the highest mortality.

ENDOMETRIAL CANCER

Type I endometrioid adenocarcinomas derive from atypical endometrial hyperplasia and are the most common female reproductive cancer in the United States. Type II cancers derive from serous or clear cell histology (see Table 2.11-12). Although type II cancers tend to be more aggressive, diagnosis and management are similar for both types. Type 1 is the most curable gynecologic cancer.

TABLE 2.11-12. Types of Endometrial Cancer

VARIABLE	TYPE I: ENDOMETRIOID	TYPE II: SEROUS
Epidemiology	75% of endometrial cancers	25% of endometrial cancers
Etiology	Unopposed estrogen stimulation (eg, obesity, tamoxifen use, exogenous estrogen-only therapy)	Unrelated to estrogen; p53 mutation present in 90% of cases
Precursor lesion	Hyperplasia and atypical hyperplasia	None
Mean age at diagnosis	55 years	67 years
Prognosis	Favorable	Poor

KEY FACT

Vaginal bleeding is present in 80% of women with endometrial carcinoma, but only 5% to 10% of women with abnormal vaginal bleeding have endometrial cancer.

History/PE

- Vaginal bleeding (early finding)
- Pain (late finding)

Diagnosis

- First, physical examination and pregnancy test if premenopausal.
- Second, ultrasonography. If postmenopausal, can do transvaginal and evaluate endometrial stripe (<4 mm unlikely to be endometrial cancer). Ultrasonography shows thickened endometrium with hypertrophy and neoplastic change in very advanced cases (Fig. 2.11-13).

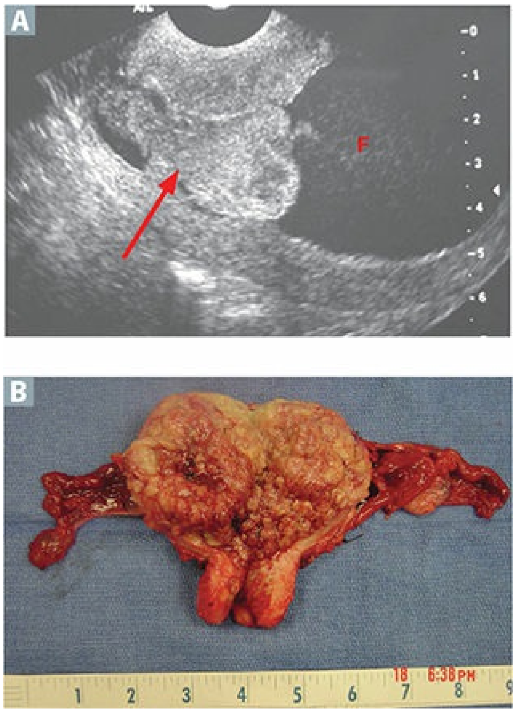


FIGURE 2.11-13. **Endometrial cancer.** **(A)** Sagittal endovaginal ultrasonogram demonstrates a mass (*arrow*) in the lower uterine segment of the endometrial canal, with fluid (*F*) distending the canal in the fundus. **(B)** Gross specimen from a different patient shows a large mass filling the endometrial canal and invading the myometrium. (Image A reproduced with permission from USMLE-Rx.com. Image B reproduced with permission from Schorge JO et al. *Williams Gynecology*. New York, NY: McGraw-Hill; 2008.)

- Finally, endometrial biopsy. If patient is postmenopausal with recurrent or persistent bleeding, a biopsy is necessary, regardless of ultrasonography results.

KEY FACT

Hormonal contraceptives reduce the risk for endometrial cancer.

KEY FACT

When to perform a biopsy for endometrial cancer:

- Postmenopausal: Endometrial stripe >4 mm or any recurrent or persistent bleeding, spotting regardless of ultrasound results
- Premenopausal: Sustained intermenstrual bleeding, menorrhagia, or amenorrhea after initial workup and in the setting of unopposed estrogen (obesity, DM)

Treatment

- High-dose progestins for women who desire future fertility
- Hysterectomy and BSO ± radiation for postmenopausal women
- Hysterectomy and BSO with adjuvant chemotherapy and/or radiation for advanced-stage cancer

CERVICAL CANCER

The endocervix lies proximal to the external os, is nonvisible, and is composed of columnar cells (similar to the lower uterine segment). The ectocervix is visible and composed of squamous cells (similar to the vagina). The exposure of columnar cells to an acidic vaginal pH results in metaplasia to squamous cells. The normal squamocolumnar junction (transformation zone) is in the ectocervix and can be exposed to carcinogens, resulting in cervical intraepithelial neoplasia (CIN), an abnormal proliferation or overgrowth of the basal cell layer.

- Human papillomavirus (HPV) DNA is found in 99.7% of all cervical carcinomas. HPV 16 is the most prevalent type in squamous cell carcinoma; HPV 18 is most prevalent in adenocarcinoma.
- Additional risk factors include immunosuppression; infection with HIV; or a history of STIs, tobacco use, or high parity.
- HPV vaccine protects against nine different pathogenic strains, including HPV types 6 and 11 (cause 90% of genital warts) and 16 and 18 (causes 70% of cervical cancer). The vaccine is recommended for males and females 11 to 26 years of age and may be considered in certain high-risk patients up to age 45.

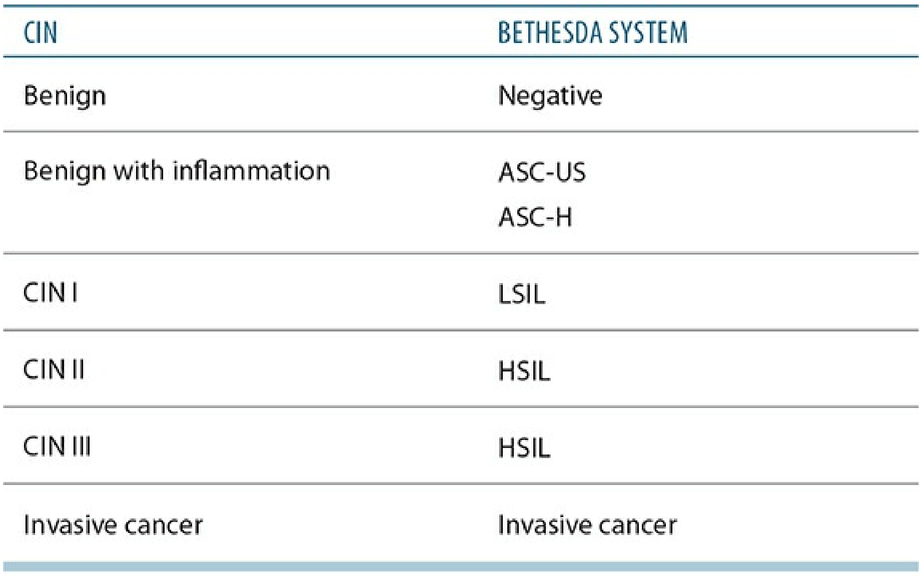
History/PE

- Intermenstrual bleeding, postcoital spotting, and cervical ulceration are the most common signs.
- Bloody or purulent, malodorous, nonpruritic discharge may appear after invasion.

Screening

- The American College of Obstetricians and Gynecologists (ACOG) currently recommends that screening for cervical cancer begin at 21 years of age regardless of onset of sexual activity.
- Screening recommendations for females with previously normal examinations:
    - 21 to 29 years of age: Pap smear (cytology) every 3 years
    - 30 to 65 years of age: Pap smear every 3 years or cotesting (Pap smear + HPV test) every 5 years
    - 65 years of age: Stoppage of screening if prior tests were negative
    - See Table 2.11-13 for classification systems of Pap smears

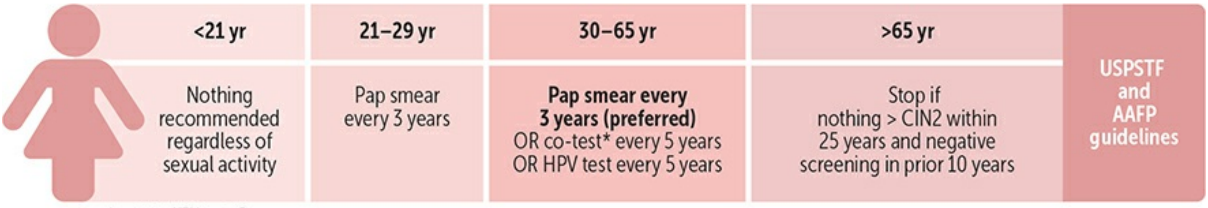
TABLE 2.11-13. Classification of Pap Smears



CIN	BETHESDA SYSTEM
Benign	Negative
Benign with inflammation	ASC-US ASC-H
CIN I	LSIL
CIN II	HSIL
CIN III	HSIL
Invasive cancer	Invasive cancer

Cervical intraepithelial neoplasia (CIN) is the histologic classification. The Bethesda system is used for reporting cytologic diagnoses.

- Alternative screening strategy using primary HPV testing to triage who should have a Pap smear (see Fig. 2.11-14)



<21 yr	21–29 yr	30–65 yr	>65 yr	USPSTF and AAFP guidelines
Nothing recommended regardless of sexual activity	Pap smear every 3 years	**Pap smear every 3 years (preferred)** OR co-test* every 5 years OR HPV test every 5 years	Stop if nothing > CIN2 within 25 years and negative screening in prior 10 years	

*co-test = HPV test + Pap smear

FIGURE 2.11-14. **Pap smear recommendations by age and HPV screening strategy.** *AAFP*, American Academy of Family Physicians; *USPSTF*, U.S. Preventive Services Task Force. (Reproduced with permission from USMLE-Rx.com.)

- Females with diethylstilbestrol (DES) exposure (risk for clear cell cancer) and/or immunocompromised status (including HIV positivity) should continue to be screened as long as they do not have a life-limiting condition.
  - Females with HIV should be screened with cytology twice in their first year after diagnosis and then annually.

Diagnosis

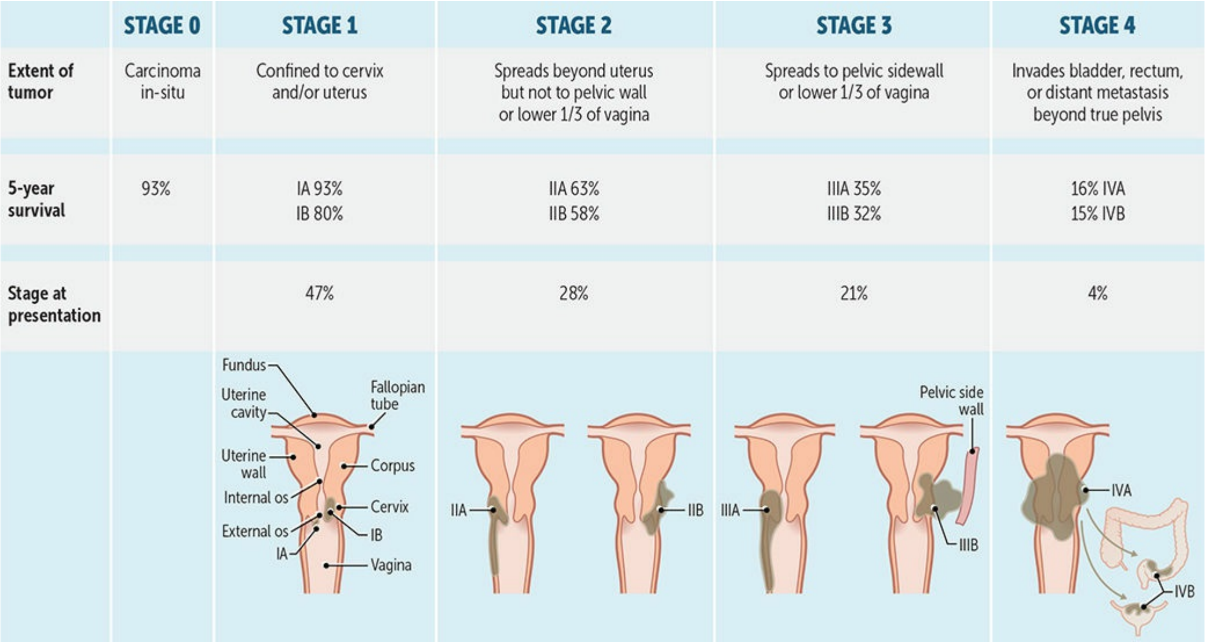
See algorithm in Figure 2.11-14. Applications of the information determine management.

- Low-grade squamous intraepithelial lesion (LSIL): Repeat Pap smear at 12 months. If ⊖ ×2, then routine screening.
- Atypical squamous cells of undetermined significance (ASC-US): Depends on cotesting; colposcopy if positive high-risk HPV.
- High-grade squamous intraepithelial lesion (LSIL): Colposcopy.

Treatment

For noninvasive disease, treatment is based on likelihood of progression to cervical cancer and patient's age/desire for future childbearing is as follows:

- **CIN I:** Observation with yearly Pap smears vs ablative therapy when done with childbearing
- **CIN II:** Observation or ablative/excisional therapy depending on childbearing status
- **CIN III:** Excisional therapy
- **Postablative or excisional therapy follow-up:**
  - CIN I, or CIN II or III with negative margins:: Pap smear at 12 months and/or HPV testing
  - CIN II or III with ⊕ margins: Pap smear at 6 months; consider a repeat endocervical curettage
- Treatment based on biopsy results for invasive disease is as follows (for staging, see Fig. 2.11-15):



	STAGE 0	STAGE 1	STAGE 2	STAGE 3	STAGE 4
Extent of tumor	Carcinoma in-situ	Confined to cervix and/or uterus	Spreads beyond uterus but not to pelvic wall or lower 1/3 of vagina	Spreads to pelvic sidewall or lower 1/3 of vagina	Invades bladder, rectum, or distant metastasis beyond true pelvis
5-year survival	93%	IA 93% IB 80%	IIA 63% IIB 58%	IIIA 35% IIIB 32%	16% IVA 15% IVB
Stage at presentation		47%	28%	21%	4%

FIGURE 2.11-15. **Staging of cervical cancer.** Anatomic display of the stages of cervical cancer, defined by location, extent of tumor, frequency of presentation, and 5-year survival. (Reproduced with permission from USMLE-Rx.com.)

  - Microinvasive carcinoma (stage IA1): Treat with cone biopsy and close follow-up or simple hysterectomy.
  - Stages IA2, IB1, IB2, IIA: May be treated either with radical hysterectomy or with radiation therapy plus chemotherapy.
  - Stages IIB, III, IV: Treat with radiation therapy plus concurrent cisplatin-based chemotherapy.

Prognosis

Five-year survival rates are inversely proportionate to the stage of cancer, with state 1A having more than 95% survival and state IV having <20% survival.

VULVAR CANCER

Risk factors include HPV (types 16, 18, and 31), lichen sclerosus, diabetes, obesity, hypertension, cardiovascular disease, smoking, high-risk sexual behavior, and immunosuppression. Vulvar intraepithelial neoplasia (VIN) is precancerous and is more commonly found in premenopausal women.

History/PE

- Presents with pruritus, pain, or ulceration of the mass
- Additional symptoms that include the following:
  - Early: Lesions that appear white, pigmented, raised, thickened, nodular, or ulcerative
  - Late: Presents with a large and cauliflowerlike or hard and ulcerated area in the vulva

Diagnosis

Vulvar punch biopsy for any suspicious lesions or persistent vulvar pruritus, especially in postmenopausal patients

Treatment

- **High-grade VIN:** Topical chemotherapy, laser ablation, wide local excision, skinning vulvectomy, and simple vulvectomy
- **Invasive:**
  - Radical vulvectomy and regional lymphadenectomy
  - Wide local excision of the primary tumor with inguinal lymph node dissection ± preoperative radiation, chemotherapy, or both

VAGINAL CANCER

Accounts for 1% to 2% of all gynecologic malignancies. Risk factors include immunosuppression, chronic irritation (eg, long-term pessary use or prolapse of female organs), low socioeconomic status, radiation for cervical cancer, hysterectomy for dysplasia, multiple sexual partners, and DES exposure. Etiologies are as follows:

- **Postmenopausal females:** Usually squamous cell carcinoma
- **Younger females:** Usually other histologic types (eg, adenocarcinoma, clear cell adenocarcinoma from DES)

History/PE

- Presents with abnormal vaginal bleeding, abnormal discharge, or postcoital bleeding
- Found in the upper third of the vagina in 75% of patients

Diagnosis

Definitive diagnosis is with biopsy and staging.

Treatment

- Local excision of involved areas when they are few and small
- Partial or complete vaginectomy—if extensive involvement of the vaginal mucosa
- Radiation therapy or radical surgery—if invasive disease

OVARIAN CANCER

Most ovarian tumors are benign, but malignant tumors are the leading cause of death from reproductive tract cancer. There is no screening test for ovarian cancer. Risk factors include the following:

- Age, low parity, ↓ fertility, or delayed childbearing.
- ⊕ family history: Patients with one affected first-degree relative have a 5% lifetime risk. With two or more affected first-degree relatives, the risk is 7%.
- Genetics: The *BRCA1* mutation carries a 45% lifetime risk for ovarian cancer. The *BRCA2* mutation is associated with a 25% lifetime risk.
- Lynch II syndrome: Also known as hereditary nonpolyposis colorectal cancer (HNPCC), it is associated with an ↑ risk for colon, ovarian, endometrial, and breast cancers.

  OCPs taken for 5 years or more ↓ risk by 29%.

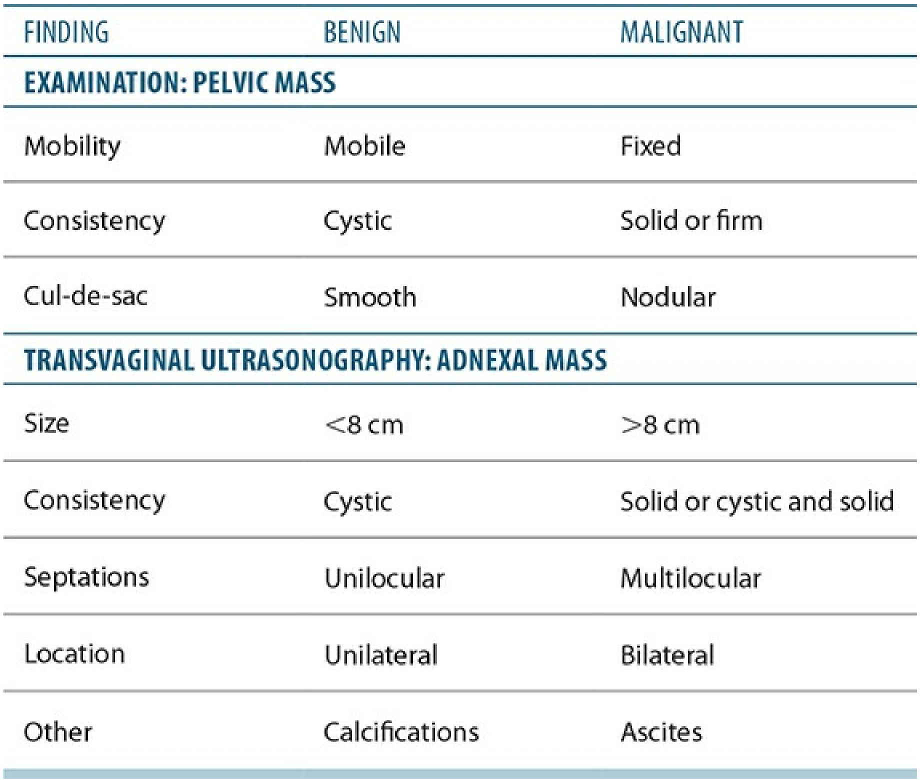
KEY FACT

Frequency of female genital tract cancers: Endometrial > ovarian > cervical
Number of deaths: Ovarian > endometrial > cervical

History/PE

- Both benign and malignant ovarian neoplasms are generally asymptomatic.
- Mild, nonspecific gastrointestinal (GI) symptoms or pelvic pressure/pain may be seen.
- Early disease is typically not detected on routine pelvic exam.
- Some 75% of women present with advanced malignant disease, as evidenced by abdominal pain and bloating, a palpable abdominal mass, and ascites.
- Table 2.11-14 differentiates the benign and malignant characteristics of pelvic masses.

TABLE 2.11-14. Benign vs Malignant Pelvic Masses



FINDING	BENIGN	MALIGNANT
EXAMINATION: PELVIC MASS		
Mobility	Mobile	Fixed
Consistency	Cystic	Solid or firm
Cul-de-sac	Smooth	Nodular
TRANSVAGINAL ULTRASONOGRAPHY: ADNEXAL MASS		
Size	<8 cm	>8 cm
Consistency	Cystic	Solid or cystic and solid
Septations	Unilocular	Multilocular
Location	Unilateral	Bilateral
Other	Calcifications	Ascites

Diagnosis

- **Tumor markers** (see Table 2.11-15): ↑ CA-125 is associated with epithelial cell cancer (90% of ovarian cancers), but is used only as a marker for progression and recurrence.

TABLE 2.11-15. **Ovarian Tumor Characteristics**

TUMOR	MARKER	CHARACTERISTICS
Epithelial	CA-125	Serous adenocarcinoma—the most common. A tumor may present with abdominal distention, bowel obstruction, and adnexal mass.
Endodermal sinus (yolk sac)	α-Fetoprotein (AFP)	Very aggressive. An endodermal sinus may be seen in ovaries and/or sacrococcygeal area in young children; gross examination shows a yellow, friable, solid mass.
Embryonal carcinoma	AFP, β-hCG	Very rare. Embryonal carcinoma may be seen in adolescents; it may present with precocious puberty and abnormal uterine bleeding.
Choriocarcinoma	β-hCG	Can develop during or after pregnancy and after molar pregnancies. This is a malignancy of trophoblastic tissue. Choriocarcinoma may be associated with bilateral theca-lutein cysts. It spreads hematogenously.
Dysgerminoma	Lactate dehydrogenase (LDH)	Most commonly seen in adolescents with sheets of uniform "fried egg" cells.
Granulosa cell	Inhibin	Most common malignant stromal tumor. Granulosa cells are often seen in females in their 50s; production of estrogen and/or progesterone may lead to postmenopausal bleeding, Call-Exner bodies on histology.

  - **Premenopausal women:** ↑ CA-125 may point to benign disease such as endometriosis or a tubo-ovarian abscess (TOA).
  - **Postmenopausal women:** ↑ CA-125 (>35 units) indicates an ↑ likelihood that the ovarian tumor is malignant.
- **Transvaginal ultrasonography:** Used to screen high-risk patients and as the first step in the workup of symptomatic females (eg, pelvic fullness, pelvic pain). A solid mass with thick septations ± ascites on ultrasound is highly suggestive of neoplasm.

KEY FACT

Granulosa cell tumors predispose to endometrial hyperplasia and carcinoma because of unopposed estrogen secretion.

KEY FACT

Any ovarian or adnexal mass in a premenarchal or postmenopausal patient is suggestive of an ovarian neoplasm.

Treatment

Ovarian masses in premenarchal females: Masses >2 cm in diameter require close clinical follow-up and often surgical removal.

Ovarian masses in premenopausal females:

- Observation is appropriate for asymptomatic, mobile, unilateral, simple cystic masses <8 to 10 cm in diameter. Most resolve spontaneously.
- Surgical evaluation of masses >8 to 10 cm in diameter and those that are complex and/or unchanged on repeat pelvic examinations and ultrasonography.

Ovarian masses in postmenopausal females:

- Closely follow with ultrasonography asymptomatic, unilateral simple cysts <5 cm in diameter with a normal CA-125.
- Surgically evaluate palpable masses.

Ovarian cancer treatment:

- **Surgery:**
  - Surgical staging: Hysterectomy/BSO with omentectomy and pelvic and paraaortic lymphadenectomy
  - Benign neoplasms warrant tumor removal or unilateral oophorectomy
- **Perioperative chemotherapy:** Routine except for females with early-stage or low-grade ovarian cancer
- **Radiation therapy:** Reserved for advanced germ cell tumors, in particular dysgerminomas (not effective in epithelial ovarian cancer)

Prevention

- Females with the *BRCA1* gene mutation should be screened every 6 months with ultrasonography and CA-125 testing. Prophylactic oophorectomy is recommended by 40 years of age or whenever childbearing is completed.
- OCP use ↓ the risk for ovarian cancer.
- There is no routine screening for ovarian cancer.

UROLOGIC GYNECOLOGY

PELVIC ORGAN PROLAPSE

Risk factors for pelvic organ prolapse include multiple vaginal deliveries, genetic predisposition, advancing age, prior pelvic surgery (hysterectomy), connective tissue disorders, and ↑ intra-abdominal pressure associated with obesity or straining with chronic constipation.

History/PE

- Presents with the sensation of a bulge or protrusion in the vagina (see Fig. 2.11-16).

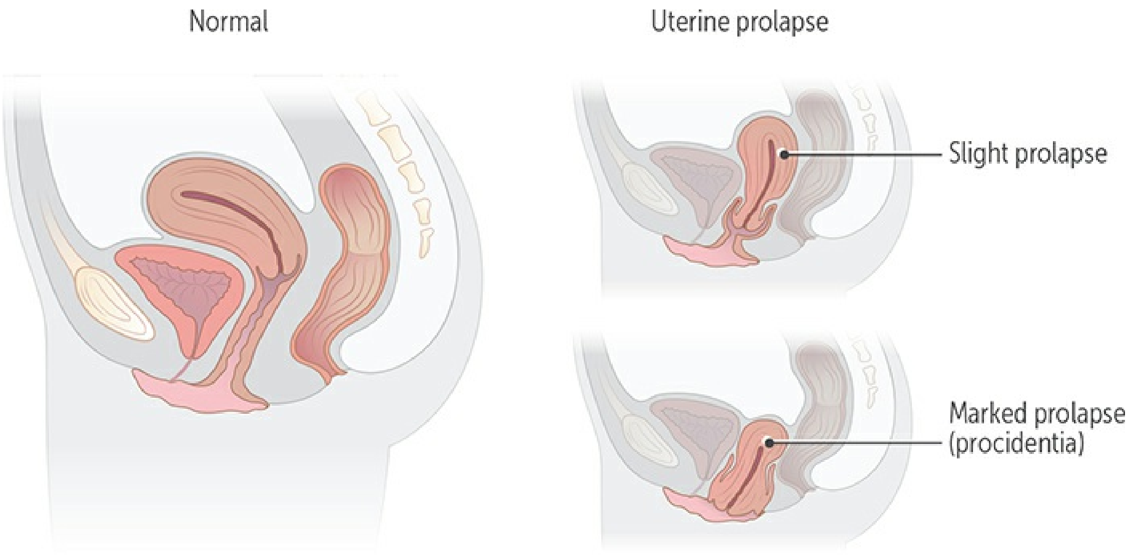


FIGURE 2.11-16. Uterine prolapse. Diagrams depicting different degrees of uterine prolapse. (Reproduced with permission from USMLE-Rx.com.)

- Urinary or fecal incontinence, a sense of incomplete bladder emptying, and/or dyspareunia are also seen.

Diagnosis

The degree of prolapse can be evaluated by having the patient perform the Valsalva maneuver while in the lithotomy position.

Treatment

- Supportive measures include a high-fiber diet, weight reduction in obese patients, and limitations on straining and lifting.
- Pessaries may reduce prolapse and are helpful in patients who do not wish to undergo surgery or in those for whom surgery is contraindicated.
- Surgical procedure depends on where the prolapse is located:
    - Uterine prolapse is treated by a hysterectomy with vaginal vault suspension.
    - Anterior/posterior vaginal wall: A prolapse here calls for repair of the anterior or posterior wall (colporrhaphy).

SEXUAL DISORDERS

GENITOPELVIC PAIN DISORDER (VAGINISMUS)

Involuntary spasm of outer one third of the vagina

History/PE

- Some caused by situational/psychosocial causes

- Can be associated with gynecologic disorders, chronic medical conditions, or certain medications

Treatment

- Most effective—cognitive and behavioral psychotherapy with systematic desensitization
- Deep muscle relaxation techniques and dilators

VULVODYNIA

Localized pain of the vulva, usually pain with insertion/at introitus.

History/PE

Typically chronic and idiopathic

Treatment

- At start of treatment: Detailed history and physical examination
- Multidisciplinary treatment with pelvic floor physical therapy and counseling

FEMALE SEXUAL INTEREST/AROUSAL DISORDER

Inability to complete sexual activity

History/PE

- Common in patients with depression or chronic disease
- Common in younger patients due to situational circumstances or depression

Treatment

- Usually resolves when underlying condition or medication is adjusted
- Individual or couples psychotherapy

NOTES

HIGH-YIELD FACTS IN

PEDIATRICS

Child Development
- DEVELOPMENTAL MILESTONES
- PRIMITIVE REFLEXES
- GROWTH
- SEXUAL DEVELOPMENT

Genetic Disease
- CYSTIC FIBROSIS

Neonatology
- APGAR SCORING
- CONGENITAL MALFORMATIONS
- NEONATAL JAUNDICE
- RESPIRATORY DISTRESS SYNDROME
- GERMINAL MATRIX HEMORRHAGE
- APNEA OF PREMATURITY
- NEONATAL EXTRACRANIAL INJURIES
- CONGENITAL HYPOTHYROIDISM
- BENIGN NEONATAL RASHES
- NEONATAL ABSTINENCE SYNDROME

Congenital Heart Disease
- ACYANOTIC CONGENITAL HEART LEFT-TO-RIGHT SHUNTS
- SEPTAL DEFECTS
- PATENT DUCTUS ARTERIOSUS
- COARCTATION OF THE AORTA
- CYANOTIC CONGENITAL HEART RIGHT-TO-LEFT SHUNTS
- TRANSPOSITION OF THE GREAT ARTERIES
- TETRALOGY OF FALLOT

Pediatric Gastrointestinal Disease
- PYLORIC STENOSIS
- INTUSSUSCEPTION
- MALROTATION WITH VOLVULUS
- MECKEL DIVERTICULUM
- HIRSCHSPRUNG DISEASE
- NECROTIZING ENTEROCOLITIS
- FOOD PROTEIN–INDUCED ALLERGIC PROCTOCOLITIS
- PEDIATRIC CONSTIPATION

Pediatric Urology
- VESICOURETERAL REFLUX
- CRYPTORCHIDISM
- INGUINAL HERNIA

- HYPOSPADIAS AND EPISPADIAS

Pediatric Immunology
- IMMUNODEFICIENCY DISORDERS
- KAWASAKI DISEASE
- JUVENILE IDIOPATHIC ARTHRITIS

Pediatric Infectious Disease
- ACUTE OTITIS MEDIA
- BRONCHIOLITIS
- CROUP (LARYNGOTRACHEOBRONCHITIS)
- EPIGLOTTITIS
- MENINGITIS
- OCULAR INFECTIONS OF THE NEONATE
- PERTUSSIS (WHOOPING COUGH)
- VIRAL EXANTHEMS
- TORCH INFECTIONS
- PINWORM INFECTION
- NEONATAL FEVER (<28 DAYS OLD)
- FEVER OF UNKNOWN ORIGIN

Pediatric Neurologic Disease
- CEREBRAL PALSY
- FEBRILE SEIZURES
- INFANTILE HYPOTONIA
- COMMON BRAIN NEOPLASMS IN CHILDREN
- SPINAL DYSRAPHISM
- BREATH-HOLDING SPELLS
- RETT SYNDROME
- CHIARI MALFORMATIONS
- BENIGN FAMILIAL MICROCEPHALY AND MACROCEPHALY

Pediatric Hematology
- DIAMOND-BLACKFAN ANEMIA
- FANCONI ANEMIA
- CYCLIC NEUTROPENIA
- THROMBOCYTOPENIA ABSENT RADIUS SYNDROME
- KASABACH-MERRITT SYNDROME
- SICKLE CELL DISEASE

Pediatric Oncology
- LEUKEMIA
- NEUROBLASTOMA
- WILMS TUMOR
- CHILDHOOD BONE TUMORS
- LANGERHANS HISTIOCYTOSIS

Pediatric Musculoskeletal Disorders
- COMMON PEDIATRIC ORTHOPEDIC INJURIES

- DUCHENNE MUSCULAR DYSTROPHY
- MYOTONIC DYSTROPHY
- SPONDYLOLISTHESIS
- METATARSUS ADDUCTUS
- CLUBFOOT (TALIPES EQUINOVARUS)
- DEVELOPMENTAL DYSPLASIA OF THE HIP
- LEGG-CALVÉ-PERTHES DISEASE
- SLIPPED CAPITAL FEMORAL EPIPHYSIS
- SCOLIOSIS

Child Abuse

Well-Child Care
- ANTICIPATORY GUIDANCE
- HEARING AND VISION SCREENING
- CHILDHOOD VACCINATIONS
- LEAD POISONING
- PERIANAL DERMATITIS
- PIGMENTED LESIONS IN CHILDHOOD

CHILD DEVELOPMENT

Pediatric development and growth are very important factors that strongly influence the well-being of the future adult. Although each child may develop differently, certain milestones and growth standards are applicable to most children.

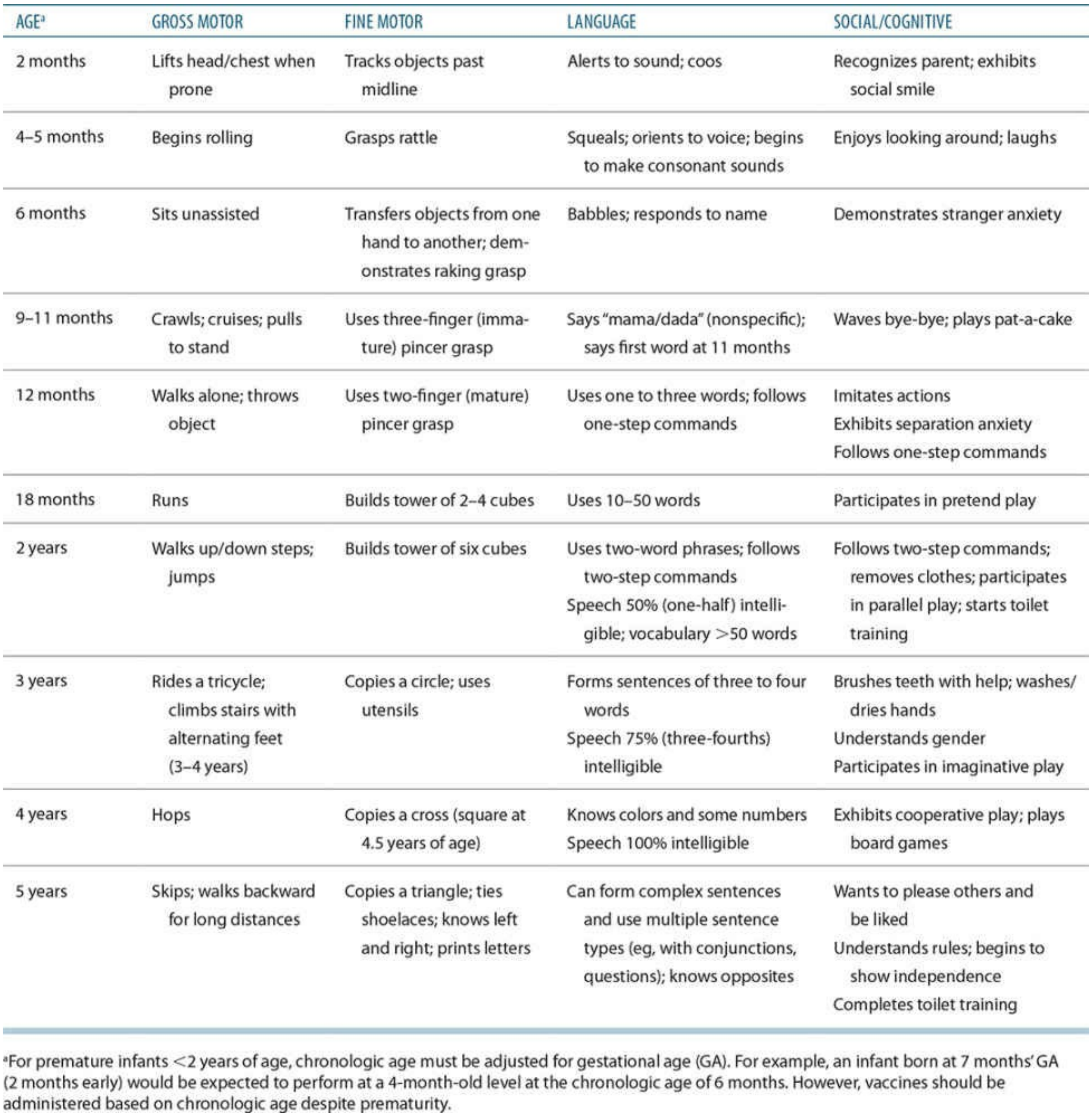
KEY FACT

Some signs that may be concerning for autism spectrum disorder include failure to achieve certain language milestones (eg, babbling/gesturing by 12 months of age, use of two-word phases by 24 months of age), impaired social interaction, restricted interest in objects/activities, and insistence on routine.

DEVELOPMENTAL MILESTONES

Assessed at routine well-child visits through age 6 years. Within each type of milestone (Table 2.12-1), two or more delays indicate a developmental delay of that type (eg, language delay). Delays in two or more types of development indicate a “global developmental delay.” Table 2.12-1 highlights major developmental milestones. If isolated language delay is present, audiology should be considered.

TABLE 2.12-1. Developmental Milestones



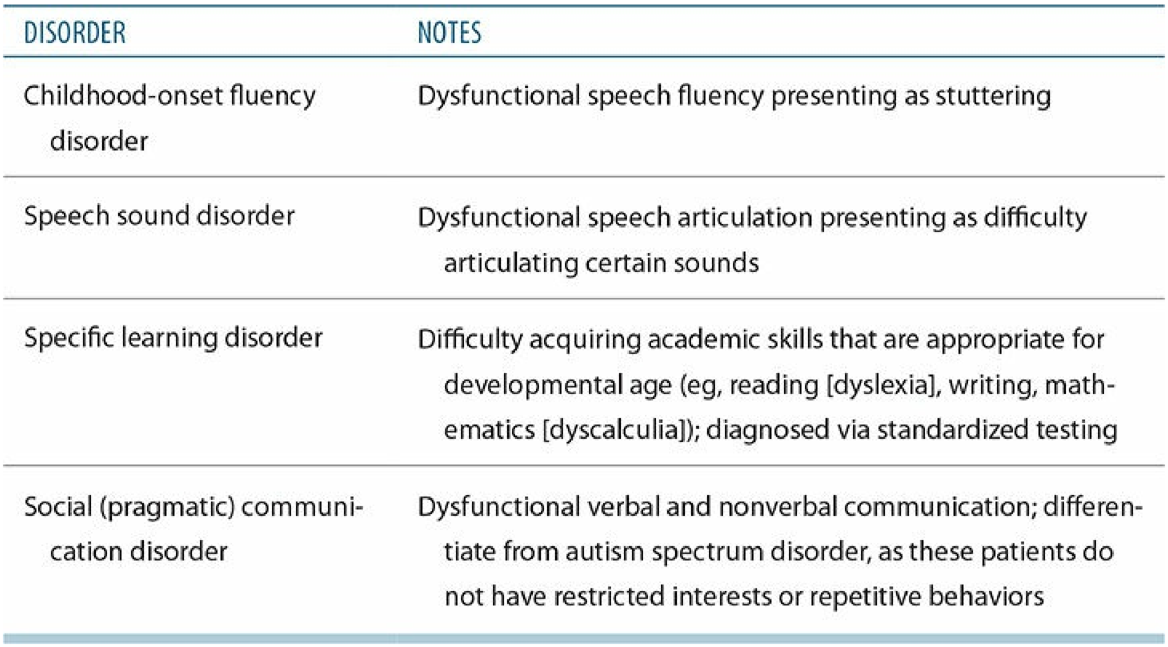
AGE[a]	GROSS MOTOR	FINE MOTOR	LANGUAGE	SOCIAL/COGNITIVE
2 months	Lifts head/chest when prone	Tracks objects past midline	Alerts to sound; coos	Recognizes parent; exhibits social smile
4–5 months	Begins rolling	Grasps rattle	Squeals; orients to voice; begins to make consonant sounds	Enjoys looking around; laughs
6 months	Sits unassisted	Transfers objects from one hand to another; demonstrates raking grasp	Babbles; responds to name	Demonstrates stranger anxiety
9–11 months	Crawls; cruises; pulls to stand	Uses three-finger (immature) pincer grasp	Says "mama/dada" (nonspecific); says first word at 11 months	Waves bye-bye; plays pat-a-cake
12 months	Walks alone; throws object	Uses two-finger (mature) pincer grasp	Uses one to three words; follows one-step commands	Imitates actions Exhibits separation anxiety Follows one-step commands
18 months	Runs	Builds tower of 2–4 cubes	Uses 10–50 words	Participates in pretend play
2 years	Walks up/down steps; jumps	Builds tower of six cubes	Uses two-word phrases; follows two-step commands Speech 50% (one-half) intelligible; vocabulary >50 words	Follows two-step commands; removes clothes; participates in parallel play; starts toilet training
3 years	Rides a tricycle; climbs stairs with alternating feet (3–4 years)	Copies a circle; uses utensils	Forms sentences of three to four words Speech 75% (three-fourths) intelligible	Brushes teeth with help; washes/dries hands Understands gender Participates in imaginative play
4 years	Hops	Copies a cross (square at 4.5 years of age)	Knows colors and some numbers Speech 100% intelligible	Exhibits cooperative play; plays board games
5 years	Skips; walks backward for long distances	Copies a triangle; ties shoelaces; knows left and right; prints letters	Can form complex sentences and use multiple sentence types (eg, with conjunctions, questions); knows opposites	Wants to please others and be liked Understands rules; begins to show independence Completes toilet training

[a] For premature infants <2 years of age, chronologic age must be adjusted for gestational age (GA). For example, an infant born at 7 months' GA (2 months early) would be expected to perform at a 4-month-old level at the chronologic age of 6 months. However, vaccines should be administered based on chronologic age despite prematurity.

Language disorder:

- Developmental disorder characterized by difficulty comprehending or producing language. Patients have a limited vocabulary for their age, use incorrect tenses, lack the ability to synthesize simple sentences, and may have word-finding difficulties.
- Inability to communicate their needs verbally may lead to temper tantrums or physical aggression. An undetected language disorder increases the risk of developing specific learning disorders in a school-age child. Early recognition and intervention improve outcomes. Table 2.12-2 lists similar conditions that must be differentiated.

TABLE 2.12-2. **Differential Diagnoses of Language Disorder**



DISORDER	NOTES
Childhood-onset fluency disorder	Dysfunctional speech fluency presenting as stuttering
Speech sound disorder	Dysfunctional speech articulation presenting as difficulty articulating certain sounds
Specific learning disorder	Difficulty acquiring academic skills that are appropriate for developmental age (eg, reading [dyslexia], writing, mathematics [dyscalculia]); diagnosed via standardized testing
Social (pragmatic) communication disorder	Dysfunctional verbal and nonverbal communication; differentiate from autism spectrum disorder, as these patients do not have restricted interests or repetitive behaviors

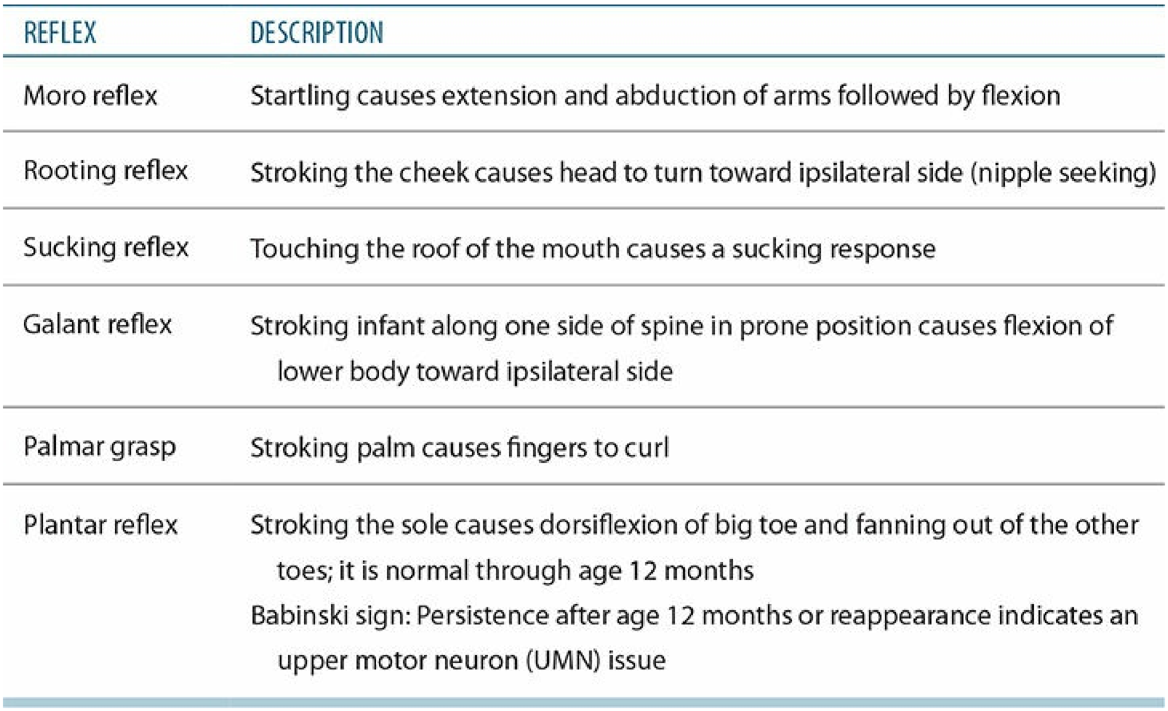
Toilet training:

- Most children start toilet training at 2 years of age.
- Bedwetting (primary nocturnal enuresis) is normal until 5 years of age. If it persists at age 6 years or older, positive reinforcement (eg, bedwetting alarms) may be considered. Desmopressin (ADH analog) and anticholinergic medications (imipramine) may be provided for refractory cases. Be sure to rule out medical conditions such as bladder dysfunction, urinary tract infection, and diabetes insipidus.

PRIMITIVE REFLEXES

Reflexes that are present during infancy and disappear with frontal lobe development. Persistence of these reflexes indicates impairment of brain development. Return of these reflexes in an adult indicates frontal lobe lesions. Table 2.12-3 outlines commonly tested reflexes.

TABLE 2.12-3. Primitive Reflexes



REFLEX	DESCRIPTION
Moro reflex	Startling causes extension and abduction of arms followed by flexion
Rooting reflex	Stroking the cheek causes head to turn toward ipsilateral side (nipple seeking)
Sucking reflex	Touching the roof of the mouth causes a sucking response
Galant reflex	Stroking infant along one side of spine in prone position causes flexion of lower body toward ipsilateral side
Palmar grasp	Stroking palm causes fingers to curl
Plantar reflex	Stroking the sole causes dorsiflexion of big toe and fanning out of the other toes; it is normal through age 12 months Babinski sign: Persistence after age 12 months or reappearance indicates an upper motor neuron (UMN) issue

GROWTH

At each well-child checkup, height and weight ± head circumference are plotted on growth charts specific for sex and age:

- **Head circumference:** Measured routinely in the first 2 years. ↑ head circumference greater than the 97th percentile is macrocephaly and may indicate hydrocephalus or tumor (may be evaluated with brain imaging); ↓ head circumference less than the 3rd percentile is microcephaly (eg, TORCH infections, fetal alcohol syndrome).
- **Height and weight:** Measured routinely until adulthood. The pattern of growth is more important than the raw numbers. Infants may lose 5% to 10% of birth weight (BW) over the first few days but should return to their BW by 14 days. Infants can be expected to double their BW by 4 to 5 months of age, triple it by 1 year of age, and quadruple it by 2 years of age.
- **Variants of normal growth:**
  - **Constitutional growth delay:** A normal variant and the most common cause of delayed puberty. The growth curve for such children lags behind that of others of the same age but remains consistent. There is often a ⊕ family history, and children ultimately achieve target height potential. The key distinguishing feature is delayed bone age until 11 years of age in girls and 13 years of age in boys.
  - **Familial short stature:** Short stature (height < second percentile) when one or both parents also have short stature. Growth curve shows a low-to-normal height velocity. Bone age corresponds with chronologic age, and puberty is not delayed. Adult height remains low.
  - **Failure to thrive (FTT):** Persistent weight for age and/or length for age less than the fifth percentile, or “falling off the growth curve” (ie, crossing two major percentile lines on a growth chart). FTT is classified as follows:
    - **Organic:** Caused by an underlying medical condition such as cystic fibrosis, congenital heart disease (CHD), milk-protein allergy, chronic infection (eg, HIV),

hypothyroidism, or gastroesophageal reflux disease (GERD)
  - **Nonorganic:** Primarily caused by psychosocial factors such as low milk supply/breastfeeding problems, inaccurate mixing of formula (too much water mixed in), maternal postpartum depression, neglect, or abuse
- **Critical to diagnosis:** A careful dietary history and close observation of parent-infant interactions. Practitioner should inquire about preparation of formula and feeding practices.
- **Diagnostic testing:** Targeted to suspected etiologies when indicated and no improvement occurs after ensuring adequate nutrition. Imaging modalities include echocardiogram for congenital heart defects and upper gastrointestinal (GI) series for GI causes.
- Children may need to be hospitalized if there is evidence of neglect or severe malnourishment. Calorie counts and supplemental nutrition (if breastfeeding is inadequate) are mainstays of treatment for nonorganic causes.

KEY FACT

Infants with FTT will first fall off the weight curve, then the height curve, and finally the head circumference curve.

KEY FACT

Newborns can lose up to 10% of their birth weight but should regain the weight by 2 weeks of life.

SEXUAL DEVELOPMENT

- **Tanner staging:** Performed to assess sexual development in boys and girls. Figure 2.12-1 illustrates the stages, Figure 2.12-2 illustrates patterns of sexual development.

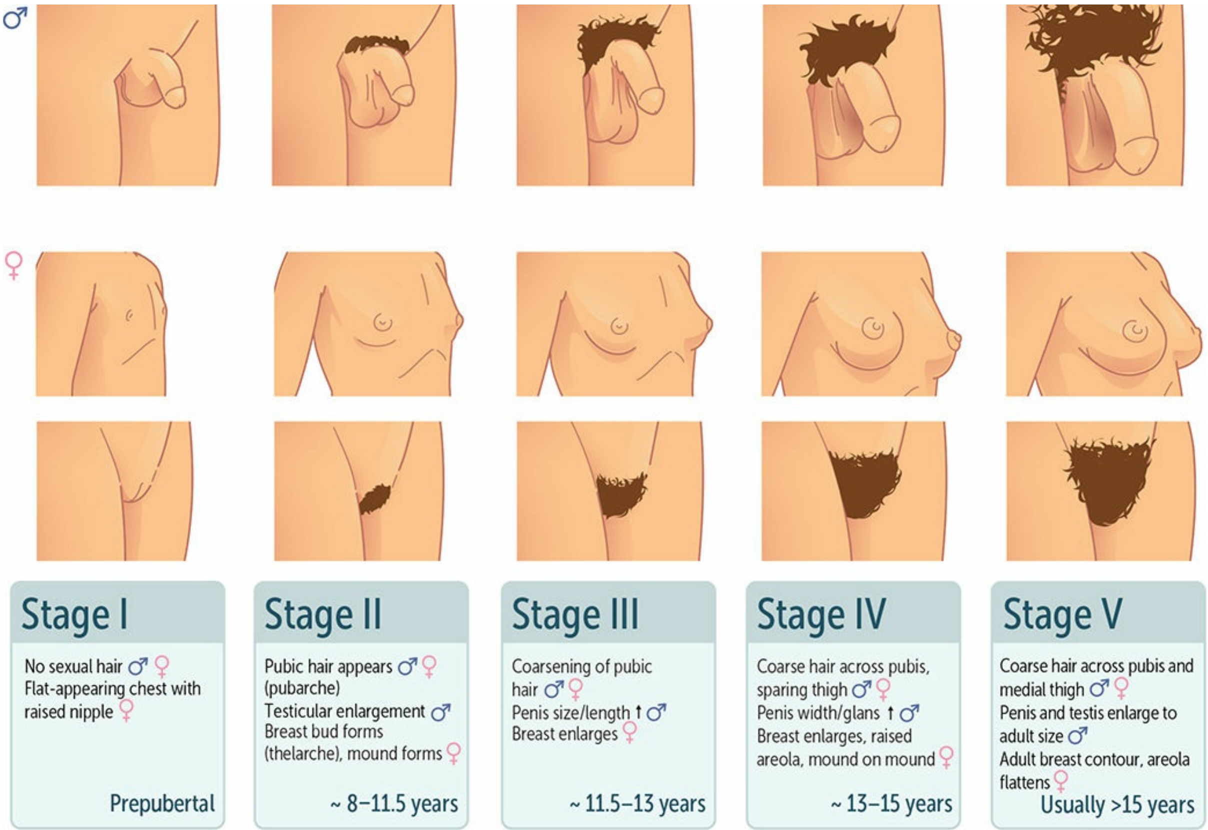

♂
♀
Stage I
No sexual hair ♂ ♀
Flat-appearing chest with raised nipple ♀
Prepubertal
Stage II
Pubic hair appears ♂ ♀ (pubarche)
Testicular enlargement ♂
Breast bud forms (thelarche), mound forms ♀
~ 8–11.5 years
Stage III
Coarsening of pubic hair ♂ ♀
Penis size/length ↑ ♂
Breast enlarges ♀
~ 11.5–13 years
Stage IV
Coarse hair across pubis, sparing thigh ♂ ♀
Penis width/glans ↑ ♂
Breast enlarges, raised areola, mound on mound ♀
~ 13–15 years
Stage V
Coarse hair across pubis and medial thigh ♂ ♀
Penis and testis enlarge to adult size ♂
Adult breast contour, areola flattens ♀
Usually >15 years

FIGURE 2.12-1. Tanner stages. The first sign of puberty in females is breast bud development; testicular enlargement is the first sign in males. (Reproduced with permission from USMLE-Rx.com.)

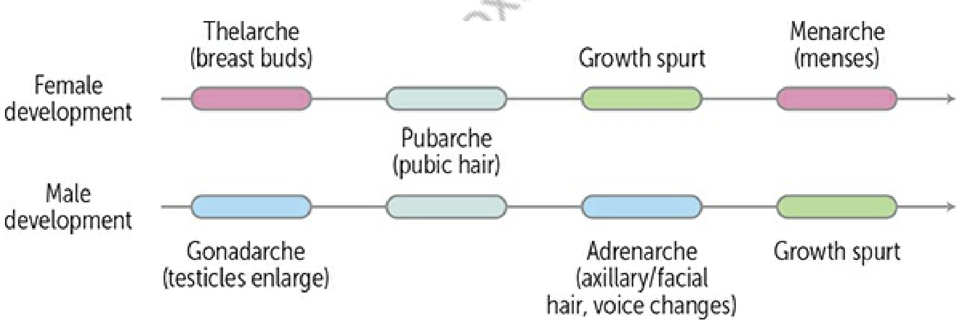

Female development
Thelarche (breast buds)
Pubarche (pubic hair)
Growth spurt
Menarche (menses)
Male development
Gonadarche (testicles enlarge)
Adrenarche (axillary/facial hair, voice changes)
Growth spurt

FIGURE 2.12-2. Patterns of sexual development in females vs males. (Reproduced with permission from USMLE-Rx.com.)

- **Variants of normal sexual development** are as follows:
  - **Precocious puberty:** Any sign of secondary sexual maturation in girls <8 years of age or boys <9 years of age. Often idiopathic; may be central or peripheral (see the Gynecology chapter)
  - **Delayed puberty:** No testicular enlargement in boys by 14 years of age or no breast development or pubic hair in girls by 13 years of age
  - **Pathologic puberty delay:** Caused by systemic disease (eg, inflammatory bowel disease [IBD]), malnutrition (eg, anorexia nervosa), gonadal dysgenesis (eg, Klinefelter syndrome, Turner syndrome), or endocrine abnormalities (eg, hypopituitarism, hypothyroidism, Kallmann syndrome, androgen insensitivity syndrome, Prader-Willi syndrome)

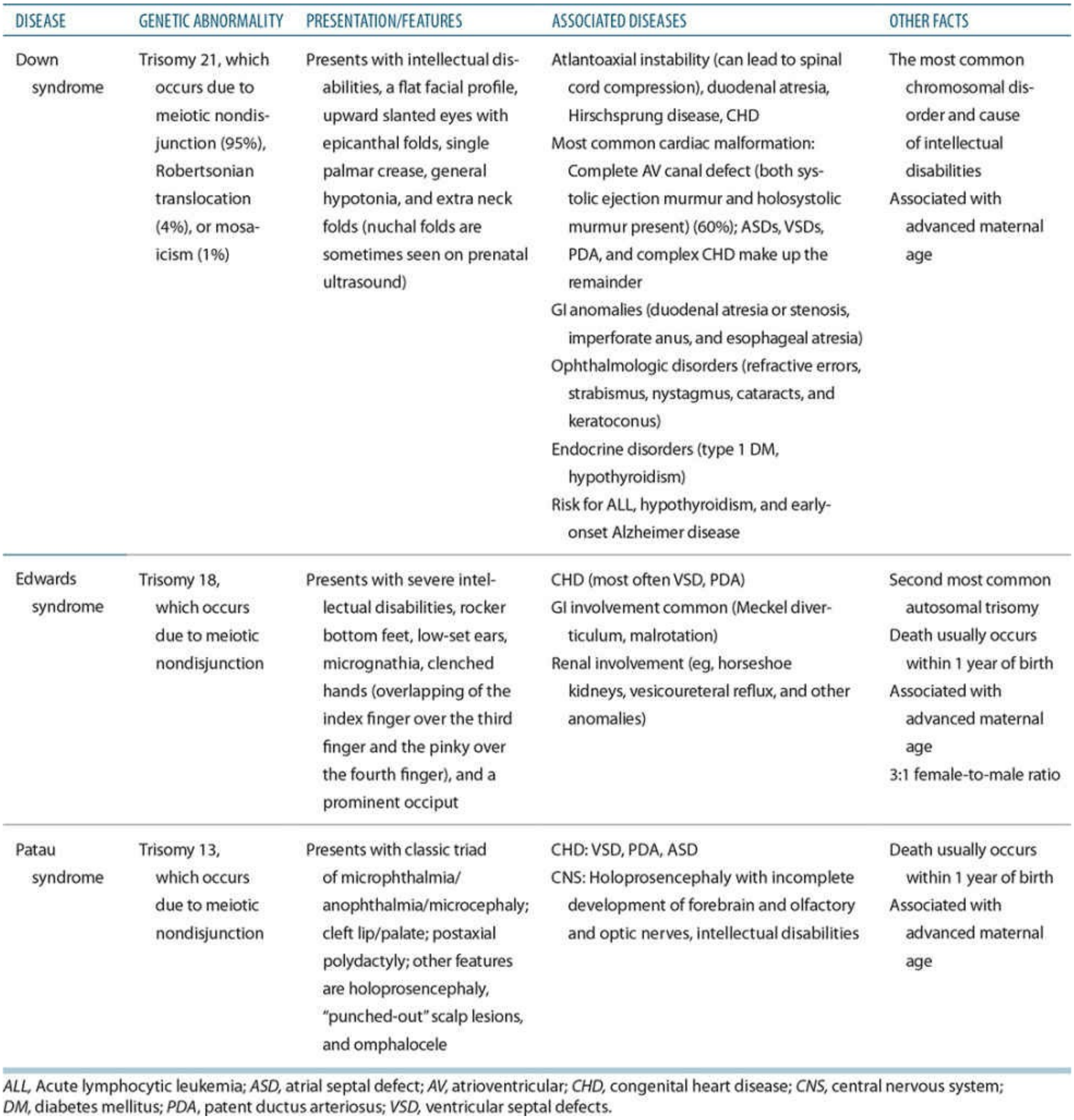
KEY FACT

Androgen insensitivity syndrome (AIS) is a genetic disorder characterized by an X-linked mutation of the androgen receptor leading to a phenotypically female appearance in a 46,XY individual. Affected individuals will have breast development, cryptorchidism, and no pubic hair. Perform a gonadectomy after puberty to prevent testicular cancer.

GENETIC DISEASE

Tables 2.12-4 to 2.12-7 outline common childhood-onset genetic diseases and their associated abnormalities.

TABLE 2.12-4. Autosomal Chromosome Abnormalities (Trisomies)



DISEASE	GENETIC ABNORMALITY	PRESENTATION/FEATURES	ASSOCIATED DISEASES	OTHER FACTS
Down syndrome	Trisomy 21, which occurs due to meiotic nondisjunction (95%), Robertsonian translocation (4%), or mosaicism (1%)	Presents with intellectual disabilities, a flat facial profile, upward slanted eyes with epicanthal folds, single palmar crease, general hypotonia, and extra neck folds (nuchal folds are sometimes seen on prenatal ultrasound)	Atlantoaxial instability (can lead to spinal cord compression), duodenal atresia, Hirschsprung disease, CHD Most common cardiac malformation: Complete AV canal defect (both systolic ejection murmur and holosystolic murmur present) (60%); ASDs, VSDs, PDA, and complex CHD make up the remainder GI anomalies (duodenal atresia or stenosis, imperforate anus, and esophageal atresia) Ophthalmologic disorders (refractive errors, strabismus, nystagmus, cataracts, and keratoconus) Endocrine disorders (type 1 DM, hypothyroidism) Risk for ALL, hypothyroidism, and early-onset Alzheimer disease	The most common chromosomal disorder and cause of intellectual disabilities Associated with advanced maternal age
Edwards syndrome	Trisomy 18, which occurs due to meiotic nondisjunction	Presents with severe intellectual disabilities, rocker bottom feet, low-set ears, micrognathia, clenched hands (overlapping of the index finger over the third finger and the pinky over the fourth finger), and a prominent occiput	CHD (most often VSD, PDA) GI involvement common (Meckel diverticulum, malrotation) Renal involvement (eg, horseshoe kidneys, vesicoureteral reflux, and other anomalies)	Second most common autosomal trisomy Death usually occurs within 1 year of birth Associated with advanced maternal age 3:1 female-to-male ratio
Patau syndrome	Trisomy 13, which occurs due to meiotic nondisjunction	Presents with classic triad of microphthalmia/anophthalmia/microcephaly; cleft lip/palate; postaxial polydactyly; other features are holoprosencephaly, "punched-out" scalp lesions, and omphalocele	CHD: VSD, PDA, ASD CNS: Holoprosencephaly with incomplete development of forebrain and olfactory and optic nerves, intellectual disabilities	Death usually occurs within 1 year of birth Associated with advanced maternal age

ALL, Acute lymphocytic leukemia; *ASD*, atrial septal defect; *AV*, atrioventricular; *CHD*, congenital heart disease; *CNS*, central nervous system; *DM*, diabetes mellitus; *PDA*, patent ductus arteriosus; *VSD*, ventricular septal defects.

TABLE 2.12-5. Sex Chromosome Abnormalities

DISEASE	GENETIC ABNORMALITY	PRESENTATION/FEATURES	ASSOCIATED DISEASES	OTHER FACTS
Klinefelter syndrome (male)	47,XXY, which occurs due to nondisjunction of sex chromosomes (maternal or paternal origin)	Presents with testicular atrophy, a eunuchoid body shape, tall stature, long extremities, gynecomastia, and female hair distribution Male newborns: Normal in phenotype with no dysmorphic features	Most common cause of primary hypogonadism in males	Characterized by the presence of an inactivated X chromosome (Barr body) ↑ risk for breast cancer, psychiatric disorders, autosomal spectrum disorders, and social problems Associated with advanced maternal age Sex chromosome karyotyping used to diagnose Treated with testosterone (prevents gynecomastia; improves secondary sexual characteristics)
Turner syndrome (female)	45,XO	Presents with short stature, shield chest, widely spaced nipples, a webbed neck, pubertal delay (due to ovarian failure), coarctation of the aorta (↓ femoral pulses), and/or bicuspid aortic valve May present with lymphedema of the hands and feet in the neonatal period	The most common cause of primary amenorrhea; caused by ovarian dysgenesis (treat with estrogen) May have horseshoe kidney	Missing one X chromosome; no Barr body Sex chromosome karyotyping used to diagnose Not associated with advanced maternal age
Double Y males	47,XYY	Often look normal; some patients very tall with severe acne (seen in 1%–2% of XYY male patients)		Observed with ↑ frequency among inmates of penal institutions Sex chromosome karyotyping used to diagnose

TABLE 2.12-6. Inherited Metabolic Disorders

DISEASE	ETIOLOGY	MODE OF INHERITANCE/NOTES
Phenylketonuria (PKU)	Caused by ↓ phenylalanine hydroxylase or ↓ tetrahydrobiopterin cofactor Tyrosine becomes essential, and phenylalanine accumulates and is subsequently converted to its ketone metabolites Not apparent at birth; presents within the first few months of life If not treated at birth, presents with intellectual disabilities, fair hair and skin, eczema, blue eyes, and a musty urine odor Associated with ↑ risk for heart disease During infancy, the patient will need special infant formula containing ↓ phenylalanine (artificial sweeteners) and ↑ tyrosine (should not breastfeed)	Autosomal recessive PKU screened for at birth

DISEASE	ETIOLOGY	MODE OF INHERITANCE/NOTES
Fabry disease	Deficiency of α-galactosidase A that leads to accumulation of ceramide trihexoside in the heart, brain, and kidneys First sign is severe neuropathic limb pain; also presents with joint swelling Skin involvement characterized by angiokeratomas and telangiectasias If untreated, findings may include chronic kidney disease presenting as proteinuria and increased risk for stroke and myocardial infarction (thromboembolic events)	X-linked recessive
Krabbe disease	Deficiency of galactosylceramide and galactoside (caused by galactosylceramidase deficiency), leading to the accumulation of galactocerebroside in the brain Characterized by progressive CNS degeneration, optic atrophy, spasticity, and death within the first 3 years of life	Autosomal recessive
Gaucher disease	Deficiency of glucocerebrosidase (also known as acid β-glucosidase) that leads to the accumulation of glucocerebroside in the brain, liver, spleen, and bone marrow May present with anemia and thrombocytopenia Infantile form manifested by early, rapid neurologic decline; adult form (more common) not manifested by brain defects; compatible with normal life span	Autosomal recessive
Niemann-Pick disease	Deficiency of sphingomyelinase that leads to the buildup of sphingomyelin cholesterol in reticuloendothelial and parenchymal cells and tissues May present with a cherry-red spot and hepatosplenomegaly	Autosomal recessive No man **Pick**s his nose with his **sphing**er
Tay-Sachs disease	Deficiency of hexosaminidase A that leads to GM_2 ganglioside accumulation Could have normal appearance until 3–6 months of age, when weakness begins and development slows and regresses An exaggerated startle response possible Presents with a cherry-red spot but no hepatosplenomegaly More prevalent in people of Jewish European descent	Autosomal recessive Tay-Sa**X** lacks he**X**osaminidase A
Metachromatic leukodystrophy	Deficiency of arylsulfatase A that leads to the accumulation of sulfatide in the brain, kidney, liver, and peripheral nerves Demyelination leading to progressive ataxia and dementia	Autosomal recessive
Hurler syndrome	Deficiency of α-L-iduronidase Leads to corneal clouding, intellectual disabilities, and gargoylism	Autosomal recessive
Hunter syndrome	Deficiency of iduronate sulfatase A mild form of Hurler syndrome with no corneal clouding and mild intellectual disabilities	
Homocystinemia	Deficiency of cystathionine synthase Causes downward lens subluxation, marfanoid body habitus, hypercoagulability, and intellectual disability Treat with anticoagulation	Autosomal recessive

TABLE 2.12-7. Other Genetic Diseases

DISEASE	FEATURES/PRESENTATION	MODE OF INHERITANCE/NOTES
Fragile X syndrome	Caused by a defect affecting the methylation and expression of the *FMR1* gene A triplet repeat disorder that may show genetic anticipation Presents in childhood; features include long and narrow face, prominent forehead and chin, large ears, testicular enlargement, and autistic behaviors	X-linked dominant The second most common genetic cause of intellectual disabilities
Friedrich ataxia	Caused by a loss-of-function mutation in frataxin (FXN) gene → trinucleotide repeat expansion of GAA →↓ expression of frataxin protein Presents in adolescence primarily with neurologic dysfunction (limb, gait ataxia) and cardiomyopathy; other features: optic atrophy, dysphagia, dysarthria, motor weakness, loss of distal proprioception, deafness, ↓ visual acuity, kyphoscoliosis, diabetes mellitus	Autosomal recessive degenerative disorder The most common hereditary ataxia
Prader-Willi syndrome	Presents with hypotonia, hyperphagia, obesity, hypogonadism, almond-shaped eyes, ↓ cognition Causes sleep apnea, DM type 2, gastric distention and rupture, and obesity-related complications	Deletion of paternal 15q11-q13 (imprinting disorder) Paternal deletion → Prader-Willi Most common syndromic form of obesity
Classic galactosemia	Caused by a deficiency of galactose-1-phosphate uridyl transferase (GALT) If not treated shortly after birth, will present in infancy with jaundice, vomiting, and hepatomegaly after feeding. Exclude galactose and lactose (galactose + glucose) from diet Late findings include cataract deposition and neurologic impairment	Autosomal recessive inheritance Most common and severe type of galactosemia Tested in newborn screening
Hereditary fructose intolerance	Deficiency in aldolase B Presents with hypoglycemia, jaundice; cirrhosis; and vomiting following consumption of fruit, juice, or honey May also present with hepatomegaly, lactic acidosis, and failure to thrive	Autosomal recessive inheritance Urine dipstick will be ⊖

MNEMONIC

Trisomies—

21—Age to **D**rink (**D**own syndrome)
18—Age to vote in **E**lections (**E**dwards syndrome)
13—Age of **P**uberty (**P**atau syndrome)

CYSTIC FIBROSIS

Autosomal recessive disorder. Mutation in cystic fibrosis transmembrane conductance regulator *(CFTR)* gene (chloride channel) on chromosome 7. Characterized by widespread exocrine gland dysfunction. Cystic fibrosis (CF) is the most common severe genetic disease in the United States and is most frequently found in Northern European ancestry.

History/PE

- Most patients are diagnosed on newborn screening.
- **Presentation:**
  - **Neonates:** Meconium ileus (obstruction of the distal ileum caused by abnormally thick meconium; 15% of presenting cases).
  - **Patients <1 year of age:** Cough, wheezing, or recurrent respiratory infections. Patients may also have steatorrhea and/or FTT.
  - **Most patients >1 year of age:** FTT (caused by pancreatic insufficiency) or chronic sinopulmonary disease/sputum production.
- Affected individuals exhibit recurrent pulmonary infections (especially with *Pseudomonas* as adults and *Staphylococcus aureus* as children) with subsequent cyanosis, digital clubbing, chronic cough (the most common pulmonary symptom), dyspnea, bronchiectasis, hemoptysis, chronic sinusitis, rhonchi, rales, and nasal polyposis.
- Patients with pancreatic insufficiency usually have greasy stools and flatulence; other prominent GI symptoms include pancreatitis, rectal prolapse, hypoproteinemia, biliary cirrhosis, jaundice, and esophageal varices.
- Patients who present later in childhood or adulthood are likely to have pancreatic manifestations predominant and have a milder pulmonary course.
- **Additional symptoms** include diabetes mellitus, "salty-tasting" skin, male infertility (agenesis of the vas deferens), and hyponatremia.
- Patients are at risk for fat-soluble vitamin deficiency (vitamins A, D, E, and K) secondary to malabsorption and may present with manifestations of these deficiencies (eg, night blindness, rickets, neuropathy, coagulopathy).

KEY FACT

Almost all cases of meconium ileus are caused by CF.

Diagnosis

Diagnostic criteria of CF include at least one of the following:

- ≥1 phenotypic feature(s) of CF
  - Chronic pulmonary disease
  - Chronic sinusitis
  - GI and nutritional abnormalities
  - Salt loss syndromes
  - Obstructive azoospermia
- History of CF in sibling
- Positive newborn screening test

Q

A newborn girl presents with lymphedema of the hands and feet, ↓ femoral pulses, a webbed neck, widely spaced nipples, short fourth metacarpals, and nail dysplasia. What form of hormone replacement therapy will the child need in the future?

PLUS at least one of the following:

- ↑ sweat chloride concentration
- Two *CFTR* gene mutations
- Abnormal nasal potential difference (NPD) test

Treatment

- Pulmonary manifestations are managed with chest physical therapy, bronchodilators, corticosteroids, antibiotics (should cover *Pseudomonas* and *S. aureus; S. aureus* is the main colonizer until 20 years of age), and deoxyribonuclease (DNase).
- Administer pancreatic enzymes at mealtimes, as well as supplemental fat-soluble vitamins (A, D, E, and K) due to malabsorption.
- Nutritional counseling and support with a high-calorie and high-protein diet are essential for health maintenance.
- Patients who have severe disease but can tolerate surgery may be candidates for a lung or pancreas transplant. Life expectancy was once ~20 years of age, but with newer treatments it is increasing to past 40 years of age.
- Ivacaftor, a drug that enhances CFTR membrane localization, was recently approved to treat CF.

NEONATOLOGY

APGAR SCORING

A rapid scoring system that helps evaluate the need for neonatal resuscitation (Table 2.12-8). Each of five parameters is assigned a score of 0 to 2 at 1 and 5 minutes after birth.

TABLE 2.12-8. **Apgar Scale (evaluated at 1 and 5 minutes postpartum)**

SIGN	2 POINTS	1 POINT	0 POINTS
Activity (muscle tone)	Active movement	Arms and legs flexed	Absent
Pulse	≥100 beats per minute (bpm)	<100 bpm	Absent
Grimace (reflex irritability)	Active (sneezes, coughs, pulls away)	Some flexion of extremities	Flaccid
Appearance (skin color)	Completely pink	Pink body with blue extremities	Blue/pale all over
Respirations	Vigorous cry	Slow, irregular respirations	Absent

- **Scores of 8 to 10:** Typically reflect good cardiopulmonary adaptation
- **Scores of 4 to 7:** Indicate possible need for resuscitation; infants should be observed, stimulated, and possibly given ventilatory support
- **Scores of 0 to 3:** Indicate the need for immediate resuscitation

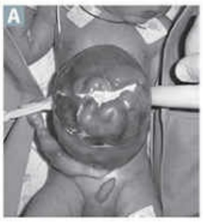
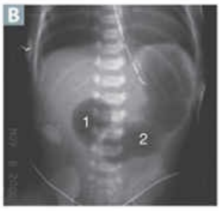
CONGENITAL MALFORMATIONS

Table 2.12-9 describes selected congenital malformations.

TABLE 2.12-9. **Selected Congenital Malformations**

MALFORMATION	PRESENTATION	DIAGNOSIS	TREATMENT
Choanal atresia	↑ nasal choanae occlusion by soft tissue, bone, or combination Chronic, recurrent purulent nasal discharge If unilateral, obstruction of affected side If bilateral, patient unable to breathe; patient is a neonatal ears, nose, and throat (ENT) emergency (baby won't be able to feed) May be associated with other anomalies—CHARGE syndrome: **C**oloboma, **H**eart disease, **A**tresia of the choanae, **R**etarded growth and mental development, **G**enital hypoplasia, and **E**ar anomalies	CT scan of and enlargement of the vomer Flexible nasal endoscopy showing point of obstruction in the nasal passage	Establishment of oral airway Surgical transnasal repair or stenting
Tracheoesophageal fistula	Tract between the trachea and esophagus Associated with defects such as esophageal atresia and **VACTERL** (**V**ertebral, **A**nal, **C**ardiac, **T**racheo**E**sophageal, **R**enal, **L**imb) anomalies Polyhydramnios in utero, oral secretions, inability to feed, gagging, aspiration pneumonia, respiratory distress	X-ray of the chest (CXR) showing a nasogastric (NG) tube coiled in the proximal atretic portion of the esophagus; this finding identifies esophageal atresia Presence of air in the GI tract suggestive; confirmation with bronchoscopy	Surgical correction
Congenital diaphragmatic hernia	GI tract segments protruding through the diaphragm into the thorax; 90% are posterior left (Bochdalek) Respiratory distress (from pulmonary hypoplasia and pulmonary hypertension); sunken abdomen; bowel sounds over the left hemithorax	Ultrasound in utero; confirmed by postnatal CXR	High-frequency ventilation or extracorporeal membrane oxygenation to manage pulmonary hypertension; surgical correction

me

MALFORMATION	PRESENTATION	DIAGNOSIS	TREATMENT
Gastroschisis	Herniation of the intestine only through the abdominal wall next to the umbilicus (usually on the right) with no sac (GI tract is exposed) Gastroschisis is commonly associated with oligohydramnios, fetal growth restriction, and prematurity; gastroschisis is less commonly associated with polyhydramnios Associated with GI stenoses or atresia Presents with erythematous; matted bowel	Diagnosis made clinically	Wrapping exposed bowel with saline-soaked gauze and securing it with plastic immediately after birth; surgical correction needed; when primary closure is not possible immediately, a silo bag can be placed to gradually reduce bowel contents into the abdomen until surgery can be performed
Omphalocele  	Herniation of abdominal viscera through the abdominal wall at the umbilicus into a sac covered by peritoneum and amniotic membrane (see Image A) Polyhydramnios in utero; often premature; associated with other GI and cardiac defects Seen in Beckwith-Wiedemann syndrome and trisomies	Diagnosis made clinically	C-section to prevent sac rupture; if the sac is intact, postpone surgical correction until the patient is fully resuscitated Keeping sac covered/stable with petroleum and gauze Intermittent NG suction to prevent abdominal distention
Duodenal atresia  	Complete or partial failure of the duodenal lumen to recanalize during gestational weeks 8–10 Polyhydramnios in utero; bilious emesis within hours after the first feeding Associated with Down syndrome and other cardiac/GI anomalies (eg, annular pancreas, malrotation, imperforate anus)	X-ray of abdomen (see Image B) showing "double bubble" sign (air bubbles in the stomach [2] and duodenum [1]) proximal to the site of the atresia	Surgical correction
Jejunal atresia	Vascular accident in utero that prevents canalization of the jejunum Caused by prenatal exposure to cocaine and other vasoconstrictive substances	"Triple bubble sign" (dilated stomach, duodenum, and proximal jejunum) may be seen	Surgical correction

Images reproduced with permission from Brunicardi FC et al. *Schwartz's Principles of Surgery*, 9th ed. New York, NY: McGraw-Hill; 2010.

KEY FACT

Omphalocele can be associated with other congenital anomalies (Beckwith-Wiedemann syndrome, trisomies 13 and 18); gastroschisis is not.

KEY FACT

Distinguishing between gastroschisis and omphalocele:

- Gastroschisis: GI contents are outside the "G" to represent lack of peritoneal covering.
- Omphalocele: GI contents sealed within the "O" to represent the presence of peritoneal covering

NEONATAL JAUNDICE

An elevated serum bilirubin concentration (>5 mg/dL) caused by ↑ hemolysis or ↓ excretion. Subtypes are as follows:

- **Conjugated (direct) hyperbilirubinemia:** Always pathologic.
- **Unconjugated (indirect) hyperbilirubinemia:** May be physiologic or pathologic. See Table 2.12-10 and Figure 2.12-3 for differentiating characteristics.

TABLE 2.12-10. Physiologic vs Pathologic Jaundice

PHYSIOLOGIC JAUNDICE	PATHOLOGIC JAUNDICE
Not present in the first 24 hours of life	Present in the first 24 hours of life
Bilirubin ↑ <5 mg/dL/day	Bilirubin ↑ >5 mg/dL/day
Bilirubin peaking at <14–15 mg/dL	Bilirubin peaks at >15 mg/dL
Direct bilirubin <10% of total	Direct bilirubin >10% of total
Resolves by 2–3 weeks in term infants	Persists beyond 2–3 weeks in term infants

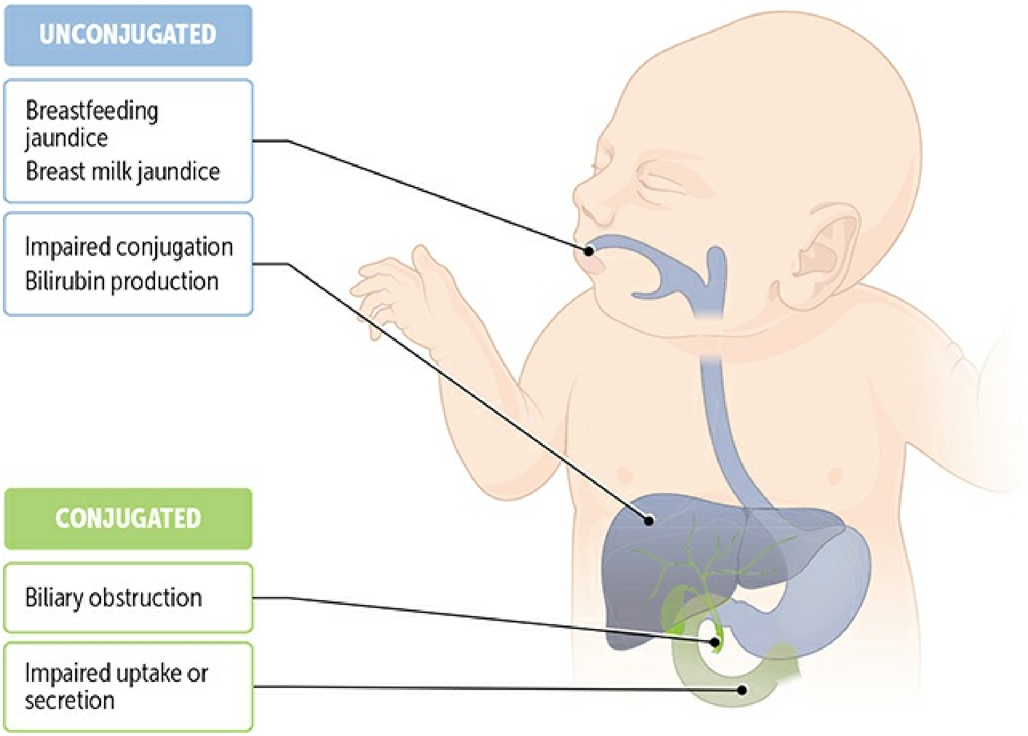

UNCONJUGATED
Breastfeeding jaundice
Breast milk jaundice
Impaired conjugation
Bilirubin production
CONJUGATED
Biliary obstruction
Impaired uptake or secretion

FIGURE 2.12-3. **Conjugated vs unconjugated hyperbilirubinemia.** (Reproduced with permission from USMLE-Rx.com.)

- **Kernicterus:** A complication of unconjugated hyperbilirubinemia that results from irreversible bilirubin deposition in the basal ganglia, pons, and cerebellum. It typically occurs at levels of >25 to 30 mg/dL and can be fatal. Risk factors include prematurity, asphyxia, and sepsis.

A

This newborn has Turner syndrome. Because of ovarian dysgenesis, the patient will require estrogen replacement therapy in the future. This newborn will need exogenous estrogen to support pubertal development and to prevent osteoporosis later in life.

MNEMONIC

***C**rigler-**N**ajjar and **G**ilbert have problems with **C**o**N**ju**G**ation of bilirubin, while **D**ubin-Johnson and **R**otor have a defective **D**oo**R** for secretion of bilirubin.*

KEY FACT

Breast milk jaundice and breastfeeding jaundice both cause increased enterohepatic circulation of unconjugated bilirubin. It is hypothesized that factors found in breast milk may inhibit hepatic enzyme UGT1A1. Breastfeeding jaundice is due to inadequate milk, → ↑ in enterohepatic circulation. Breastfeeding jaundice occurs in the first week of life, whereas breast milk jaundice peaks in the second week of life. Treatment of breastfeeding jaundice is hydration. Breast milk jaundice does not require treatment, as it resolves with time.

History/PE

See Table 2.12-11.

TABLE 2.12-11. Mechanisms of Neonatal Jaundice

MECHANISM	EXAMPLE(S)	PREDOMINANT BILIRUBIN SPECIES
↑ bilirubin production; mechanism is via hemolysis	Hemolysis (ABO or Rh incompatibility) Erythrocyte enzyme deficiency (glucose-6-phosphate dehydrogenase [G6PD] and pyruvate kinase deficiency) Erythrocyte structural defects (sickle cell anemia, hereditary spherocytosis) Ineffective erythropoiesis (thalassemias) Sepsis with disseminated intravascular coagulation (DIC)	↑ unconjugated bilirubin
Impaired conjugation of bilirubin	Gilbert syndrome Crigler-Najjar syndrome Newborn physiologic jaundice	↑ unconjugated bilirubin
Impaired bilirubin uptake and secretion from the liver	Dubin-Johnson syndrome Rotor syndrome	↑ conjugated bilirubin
↑ enterohepatic circulation	Poor feeding/breastfeeding jaundice Breast milk jaundice Dehydration	↑ unconjugated bilirubin
Obstruction of biliary tree and ↓ excretion	Biliary/choledochal cyst Biliary atresia Alagille syndrome (ie, too few bile ducts for adequate bile drainage)	↑ conjugated bilirubin

- History should focus on diet (breast milk or formula), intrauterine drug exposure, and family history (hemoglobinopathies, enzyme deficiencies, RBC defects).
- PE may reveal signs of hepatic or GI dysfunction (abdominal distention, delayed passage of meconium, light-colored stools, dark urine), infection, or birth trauma (cephalohematomas, bruising, pallor, petechiae).

- Kernicterus presents with lethargy, poor feeding, a high-pitched cry, hypertonicity, and seizures.
- Jaundice may follow a cephalopedal progression as bilirubin concentrations ↑.

Q

A 3-day-old boy born at 39 weeks' gestational age via normal spontaneous vaginal delivery has failed to pass meconium and today displays abdominal distention and five episodes of bilious vomiting. Rectal examination shows no stool in the rectal vault. Air contrast enema shows an obstruction at the ileum. What is the most likely cause of this patient's symptoms?

Diagnosis

- For indirect hyperbilirubinemia, complete blood cell count (CBC) with peripheral blood smear (abnormal RBCs and signs of hemolysis); blood typing of mother and infant (ABO or Rh incompatibility); Coombs test and bilirubin levels
- For direct hyperbilirubinemia, liver function tests (LFTs), bile acids, assess liver anatomy and biliary tract via ultrasound and/or hydroxy iminodiacetic acid (HIDA) scan can confirm suspected cholestatic disease
- A jaundiced neonate who is febrile, hypotensive, and/or tachypneic needs a full sepsis workup and intensive care unit (ICU) monitoring

Treatment

- Treat underlying causes (eg, infection).
- Treat unconjugated hyperbilirubinemia with phototherapy (for mild elevations) or exchange transfusion (for severe elevations >20 mg/dL). Start phototherapy earlier (10–15 mg/dL) for preterm infants. Phototherapy is not indicated for conjugated hyperbilirubinemia and can lead to skin bronzing.

A

This infant most likely has meconium ileus resulting from CF; however, Hirschsprung disease should remain on the differential diagnosis, as it also can cause delayed meconium passage. Meconium ileus causes obstruction at the level of the ileum, whereas Hirschsprung disease causes rectosigmoid obstruction, and a rectal exam may result in expulsion of stool.

RESPIRATORY DISTRESS SYNDROME

Respiratory distress syndrome ([RDS]; also known as neonatal respiratory distress syndrome [NRDS]) is the most common cause of respiratory failure in preterm infants (affects >70% of infants born at 28 to 30 weeks GA); it was formerly known as hyaline membrane disease. Surfactant deficiency leads to poor lung compliance, alveolar collapse, and atelectasis. Risk factors include C-section, maternal diabetes mellitus (DM), male sex, and the second born of twins.

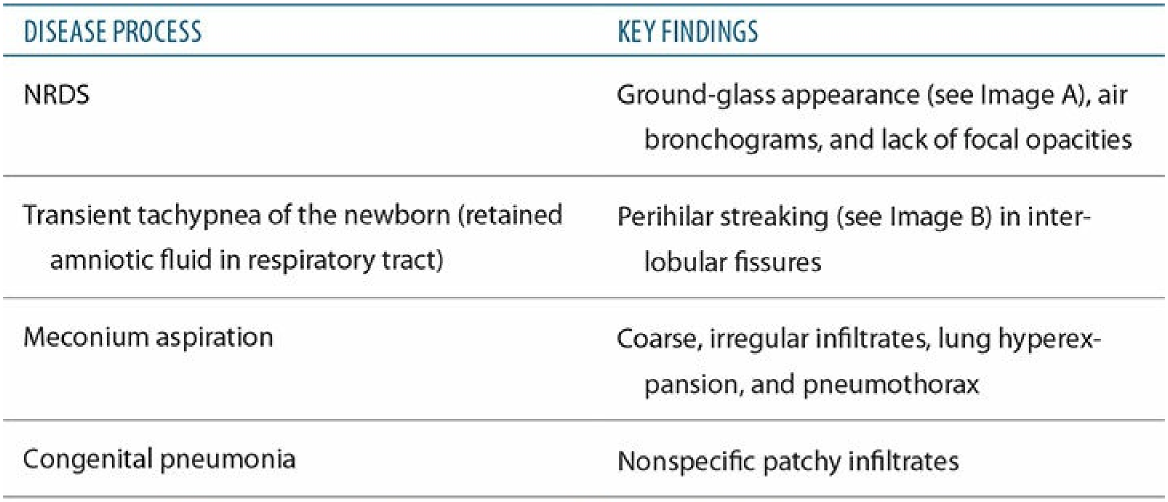
History/PE

Presents in the first 48 to 72 hours of life with a respiratory rate >60/min, progressive hypoxemia, cyanosis, nasal flaring, intercostal retractions, and expiratory grunting

Diagnosis

- Arterial blood gases (ABGs), CBC, and blood cultures to rule out infection
- Clinical diagnosis confirmed with characteristic findings on x-ray of the chest (CXR); see Table 2.12-12.

TABLE 2.12-12. X-ray of the Chest Findings in Neonatal Lung Pathology



DISEASE PROCESS	KEY FINDINGS
NRDS	Ground-glass appearance (see Image A), air bronchograms, and lack of focal opacities
Transient tachypnea of the newborn (retained amniotic fluid in respiratory tract)	Perihilar streaking (see Image B) in interlobular fissures
Meconium aspiration	Coarse, irregular infiltrates, lung hyperexpansion, and pneumothorax
Congenital pneumonia	Nonspecific patchy infiltrates

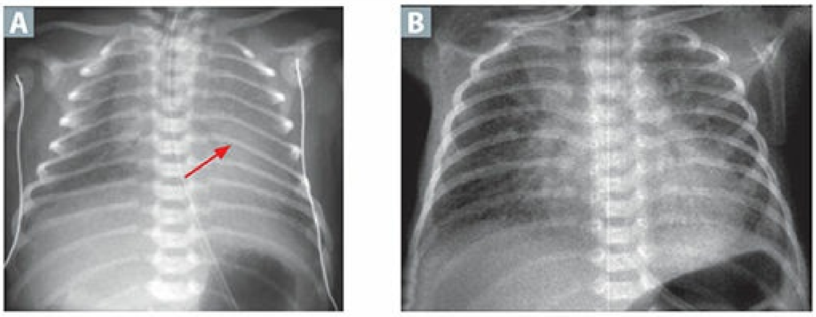


Image A reproduced with permission from Tintinalli JE et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 7th ed. New York, NY: McGraw-Hill; 2010. Image B reproduced with permission from Alorainy IA, Barlas NB, Al-Boukai AA. Pictorial essay: Infants of diabetic mothers. *Indian J Radiol Imaging*. 2010;20(3):174–181.

Treatment

- Continuous positive airway pressure (CPAP) or intubation and mechanical ventilation
- Artificial surfactant administration ↓ mortality
- Pretreatment of mothers at risk for preterm delivery (24 weeks to $33^{6}/_{7}$ weeks) in the next 7 days with corticosteroids

Complications

Persistent patent ductus arteriosus (PDA), bronchopulmonary dysplasia, retinopathy of prematurity, barotrauma from positive pressure ventilation, intraventricular hemorrhage, and necrotizing enterocolitis (NEC) are complications of treatment.

GERMINAL MATRIX HEMORRHAGE

Often occurs in preterm infants or low-BW infants due to the fragility of their germinal matrix, a highly vascular region important for fetal neural development. Caused by decreased cerebral blood flow leading to ischemia and reperfusion injury. Many cases (up to 50%) are asymptomatic. More severe cases can be characterized by hypotonia, decreased level of consciousness, seizures, and irregular respirations. Germinal matrix hemorrhage can be diagnosed with head ultrasound. Management is often supportive.

APNEA OF PREMATURITY

Intermittent cessation of respiration for >20 seconds in premature infants (gestational age <37 weeks) due to immaturity of the central respiratory centers. Affects almost all infants with a gestational age <28 weeks. Presents with episodes of intermittent apnea with bradycardia and desaturation in a premature infant who is healthy and well between episodes. Diagnosis is clinical, and alternative causes should be ruled out. Treatment involves noninvasive ventilation and methylxanthines such as caffeine, which stimulate the respiratory drive. Apnea of prematurity resolves with maturity (by 37 weeks in an infant born >28 weeks).

NEONATAL EXTRACRANIAL INJURIES

Extracranial injuries in the newborn often occur secondary to instrumentation injury during delivery. The layers of the head from outermost to innermost are skin, epicranial aponeurosis, periosteum, bone, dura mater, and arachnoid mater. Table 2.12-13 shows the commonly tested extracranial injuries.

TABLE 2.12-13. **Neonatal Extracranial Injuries**

TYPE OF INJURY	DESCRIPTION
Caput succedaneum	Edema or hematoma of the scalp that commonly occurs secondary to vacuum extraction Located above the periosteum and crosses suture lines; resolves spontaneously without treatment
Cephalhematoma	Hematoma that forms below the periosteum commonly over the parietal or occipital bone and does not cross suture lines; resolves spontaneously without treatment Complications: Infection and infant jaundice (due to breakdown of a large hematoma)
Subgaleal hemorrhage	Bleeding into the subgaleal space between the periosteum and epicranial aponeurosis (galea aponeurotica) due to injury to emissary veins by traction during delivery; presents as a fluctuant diffuse swelling that can shift with movement and crosses suture lines; the subgaleal space extends from orbital ridges anteriorly to the nape of the neck posteriorly and can hold 40% of a neonate's total blood volume, resulting in significant volume depletion and hemorrhagic shock; treatment is by volume resuscitation and correction of coagulopathy

CONGENITAL HYPOTHYROIDISM

Thyroid hormone deficiency in the neonate, often asymptomatic at birth due to transplacental transfer of maternal thyroxine. Most commonly due to thyroid dysgenesis in the United States. Other causes include thyroid agenesis, iodine deficiency (most common cause in underdeveloped countries), dyshormonogenesis (autosomal recessive), and transfer of maternal antibodies.

History/PE

- Usually asymptomatic at birth; may cause delayed passage of meconium due to decreased intestinal motility
- Manifestations after decrease of maternal thyroid hormone, including lethargy, hypotonia, large protruding tongue, umbilical hernia, enlarged fontanelle, constipation, jaundice, pale dry skin, and intellectual disability

Diagnosis

Newborn screening mandatory with thyroid-stimulating hormone (TSH) levels 24 to 48 hours. Increased TSH levels indicate hypothyroidism.

Treatment

- Levothyroxine; avoid coadministration with soy, calcium, and iron due to decreased absorption

- Untreated or delayed treatment of disease causes decreased neurocognitive function (eg, decreased intelligence quotient)

MNEMONIC

6Ps of congenital hypothyroidism—

Potbellied
Pale
Puffy face
Protruding umbilicus
Protruding tongue
Poor brain development

BENIGN NEONATAL RASHES

Table 2.12-14 lists the common benign neonatal rashes.

TABLE 2.12-14. Benign Neonatal Rashes

RASH	DESCRIPTION	MANAGEMENT
Erythema toxicum neonatorum	Onset within first 3 days of life Presents as erythematous pustules on the trunk and proximal extremities	Observation; resolves in 1 week
Milia	Presents at birth Presents as white, firm papules on the face	Observation; resolves in 1 month
Milia rubra (heat rash)	Not present at birth, can develop any time afterward Presents as erythematous papules on occluded and intertriginous areas due to blockage of eccrine sweat ducts in the setting of increased heat	Prevent overheating Topical corticosteroids if severe
Neonatal pustular melanosis	Presents at birth Presents as diffuse, nonerythematous pustules that evolve into hyperpigmented macules with a scale May involve the palms and soles	Observation, as pustules resolve within days Possible for hyperpigmentation to take months to resolve
Neonatal cephalic pustulosis (neonatal acne)	Onset around 3 weeks of age Presents as erythematous papules and pustules only on the face and scalp	Observation May take weeks to months to resolve Topical corticosteroids or ketoconazole if severe

NEONATAL ABSTINENCE SYNDROME

Withdrawal symptoms in neonates born to females with narcotic dependence during pregnancy. Newborns at high risk include those born to females with poor social support, poor mental health, no prenatal care, intravenous drug use (IVDU) infections (eg, hepatitis C), or mothers requiring chronic prescription opioids.

History/PE

- It usually presents >24 hours after birth due to withdrawal from transplacental opiates. It may present earlier if mother used heroin (short half-life).
- Central nervous symptoms (CNS) symptoms include shortened sleep-wake cycles, hypertonia, tremor, and suck-swallow incoordination.
- Autonomic symptoms include diaphoresis, sneezing, and yawning.
- Other symptoms include irritability, vomiting, and diarrhea.

Diagnosis/Treatment

- Clinical diagnosis; confirmation with drug testing of umbilical cord blood, urine, or stool
- Mild withdrawal treated with nonpharmacologic approach: Quiet environment, swaddling, small frequent feeding
- Severe withdrawal treated with morphine and methadone followed by tapering and support

CONGENITAL HEART DISEASE

Intrauterine risk factors for CHD include maternal illness (DM, phenylketonuria [PKU]), drug use (alcohol, lithium, thalidomide, phenytoin, retinoic acid), and infections (rubella). CHD can also be associated with fetal genetic syndromes. See Table 2.12-15 for a list of common associations with cardiac defects.

TABLE 2.12-15. Congenital Cardiac Defect Associations

DEFECT	ASSOCIATION
AV septal defect (endocardial cushion defect), VSD, ASD	Down syndrome
PDA, pulmonary artery stenosis, septal defects	Congenital rubella
Coarctation of the aorta, bicuspid aortic valve	Turner syndrome
DiGeorge syndrome	Truncus arteriosus, tetralogy of Fallot
Supravalvular aortic stenosis	Williams syndrome
Ebstein anomaly (apical displacement of the tricuspid valve leading to atrialization of the right ventricle)	Prenatal lithium exposure
VSD, PDA, ASD, tetralogy of Fallot	Prenatal alcohol exposure
VSD and transposition of the great arteries	Maternal diabetes during pregnancy

CHD is classified by the presence or absence of cyanosis at birth or shortly after:

- **Acyanotic CHD ("pink babies"):** Have left-to-right shunts (oxygenated blood is shunted back into the pulmonary circulation) or no shunt (eg, before congenital obstruction).
- **Cyanotic CHD ("blue babies"):** Have right-to-left shunts (deoxygenated blood is shunted into the systemic circulation). Diagnosed prenatally or immediately after birth. It usually requires urgent surgical treatment and/or maintenance of PDA.

MNEMONIC

Noncyanotic heart shunts—

The 3 Ds

VS**D**

AS**D**
P**D**A

MNEMONIC

Cyanotic heart shunts—

The 5 Ts

Truncus arteriosus
Transposition
Tricuspid atresia
Tetralogy of Fallot (TOF)
Total anomalous pulmonary venous return (TAPVR)

KEY FACT

VSD is the most common type of CHD. Ventricular septal defects occur most commonly in the membranous septum, and most resolve without intervention.

MNEMONIC

VACTERL-H includes:

Vertebral anomalies
Anal atresia
Cardiac anomalies (ASD, VSD, PDA)
Tracheal-esophageal fistula
Esophageal atresia
Renal structural anomalies
Limb anomalies, essentially radii and/or thumbs
Hydrocephalus

ACYANOTIC CONGENITAL HEART LEFT-TO-RIGHT SHUNTS

May be asymptomatic at birth. The severity of clinical presentation varies with defect size. Each has a characteristic murmur. Ventral septal defect (VSD) is the most common. PDA is less common overall but most common in prematurity. Uncorrected clinically significant left-to-right shunts → ↑ pulmonary blood flow → pathologic remodeling of vasculature → pulmonary arterial hypertension and right ventricular hypertrophy (RVH) → right-left shunt reversal (Eisenmenger syndrome).

KEY FACT

A venous hum is a benign murmur that can be present in childhood. The murmur is a low-pitched, vibratory murmur that is heard near the clavicle throughout the cardiac cycle.

Unlike the murmur of hypertrophic cardiomyopathy, a venous hum murmur is loudest when sitting and disappears with supine position or neck rotation.

SEPTAL DEFECTS

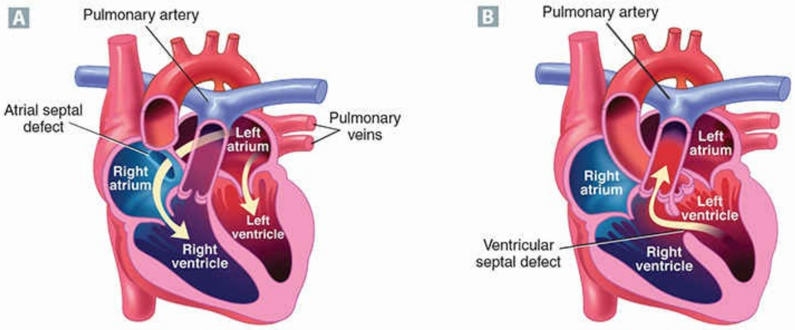
A condition in which a defective opening in the atrial (ASD) or ventricular (VSD) septum allows blood to flow between the atria or ventricles, leading to left-to-right shunting (left-side pressures > right-side pressures). VSD is the most common type of CHD.

Presentation and Diagnosis

See Table 2.12-16.

TABLE 2.12-16. **Presentation and Diagnosis of ASD vs VSD**

	ASD (SEE IMAGE A)	VSD (SEE IMAGE B)
Associated syndromes	Holt-Oram syndrome (absent radii, ASD, first-degree heart block) Fetal alcohol syndrome Trisomies (13, 18, 21) Turner syndrome	Holt-Oram syndrome Fetal alcohol syndrome Toxoplasmosis, other agents (syphilis, varicella, and zika virus), rubella, cytomegalovirus, herpes simplex (TORCH infections) Cri du chat syndrome Trisomies (13, 18, and 21) Turner syndrome
Presentation	Small defects: Asymptomatic Large defects: Easy fatiguability, FFT, recurrent respiratory infections, CHF	Small defects: Asymptomatic Large defects: Easy fatiguability, FFT, recurrent respiratory infections, CHF
Auscultation findings	Wide and fixed split S_2 Systolic ejection murmur at the upper left sternal border (↑ flow across pulmonary valve) Mid-diastolic ruble at the left sternal border (caused by increased flow across tricuspid valve)	Harsh holosystolic murmur at lower-left sternal border (louder for small defects) Narrow S_2 with ↑ P_2 (large defect) Mid-diastolic apical rumble (caused by increased flow across mitral valve)
CXR findings	Cardiomegaly ↑ pulmonary vascular markings	Cardiomegaly ↑ pulmonary vascular markings
Echocardiogram findings	Right ventricular hypertrophy Right atrial enlargement Defect and blood flow across atrial septum	Left ventricular hypertrophy (LVH) RVH may be found in large defects Defect and blood flow across ventricular septum


A
Pulmonary artery
Atrial septal defect
Pulmonary veins
Left atrium
Right atrium
Left ventricle
Right ventricle
B
Pulmonary artery
Left atrium
Right atrium
Left ventricle
Ventricular septal defect
Right ventricle

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KEY FACT

The size of the VSD is inversely proportional to the intensity of the murmur. The smaller the VSD, the more intensely the murmur will be heard.

KEY FACT

ASD has a fixed, widely split S_2.

Treatment

- Most small ASDs/VSDs close spontaneously and do not require treatment. Follow-up echocardiography is scheduled based on size of ASD/VSD and physical examination.
- Antibiotic prophylaxis is generally not needed before procedures.
- If congestive heart failure (CHF) develops, best initial treatment involves medical management of CHF, using the following:
  - Diuretics
  - Then positive inotropes and angiotensin-converting enzyme inhibitors
- Surgical correction is indicated in symptomatic patients who:
  - Fail in medical management
  - <1 year of age with signs of pulmonary hypertension
  - Older children with large defects that have not ↓ in size over time
- Early correction prevents complications such as arrhythmias, right ventricular dysfunction, and Eisenmenger syndrome

PATENT DUCTUS ARTERIOSUS

PDA (Fig. 2.12-4) is a failure of the ductus arteriosus to close completely postnatally → left-to-right shunt from the aorta to the pulmonary artery. PDA is associated with prematurity and congenital rubella syndrome.

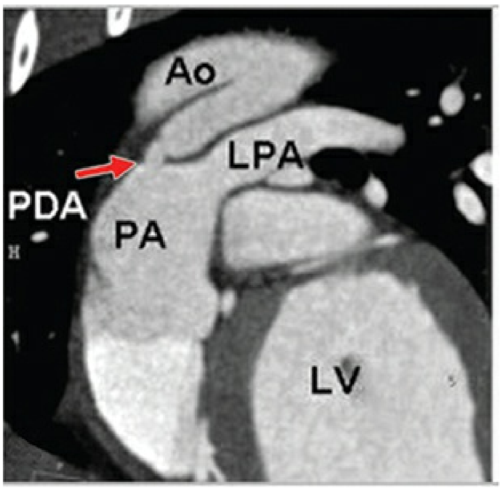


FIGURE 2.12-4. **Patent ductus arteriosus with resultant left-to-right shunting *(arrow)*.** *Ao,* Aorta; *PA,* pulmonary artery; *PDA,* patent ductus arteriosus; *LPA,* left pulmonary artery; *LV,* left ventricle. (Reproduced with permission from Henjes CR, Nolte I, Wesfaedt P. Multidetector-row computed tomography of thoracic aortic anomalies in dogs and cats: patent ductus arteriosus and vascular rings. *BMC Vet Res.* 2011;7:57. DOI: 10.1186/1746-6148-7-57.)

History/PE

- Patients with large defects may present with FTT, recurrent lower respiratory tract infections, and CHF.
- Examination reveals a continuous "machinery murmur" at the second left intercostal space at the sternal border, a loud S_2, a wide pulse pressure, and bounding peripheral pulses.
- Uncorrected PDA can eventually result in cyanosis (blue toes, normal fingers) through an Eisenmenger syndrome.

Diagnosis

- **Best initial test:** Echocardiogram will demonstrate the defect. Large PDAs will show left atrial and left ventricular enlargement.
- Doppler color flow will demonstrate blood shunting from the aorta into the pulmonary artery.
- ECG may show left ventricular hypertrophy (LVH), and CXR may reveal cardiomegaly with large PDAs.

Treatment

- Best initial treatment: Indomethacin (a nonsteroidal anti-inflammatory drug [NSAID]) unless the PDA is needed for survival (eg, transposition of the great arteries, tetralogy of Fallot [TOF], hypoplastic left heart), or if indomethacin is contraindicated (eg, intraventricular hemorrhage).
- If indomethacin fails or if the infant is >2 weeks of age, surgical closure is typically required.

MNEMONIC

*Come **IN** and **CLOSE** the door. Give **IN**domethacin to **CLOSE** a PDA.*

KEY FACT

Coarctation of the aorta and bicuspid aortic valve are associated with Turner syndrome.

KEY FACT

In infants presenting in shock within the first few weeks of life, look for:

- Sepsis
- Inborn errors of metabolism
- Ductal-dependent CHD, usually left-sided lesions
- Congenital adrenal hyperplasia

COARCTATION OF THE AORTA

Aortic narrowing near insertion of ductus arteriosus ("juxtaductal"), just distal to the left subclavian artery → ↑ flow proximal to and ↓ flow distal to the coarctation (Fig. 2.12-5). Associated with Turner syndrome, bicuspid aortic valve (found in more than two out of three cases), and intracranial aneurysms. More common among male sex. Complications include heart failure (HF), aortic rupture, endocarditis, and cerebral hemorrhage (due to berry aneurysms).

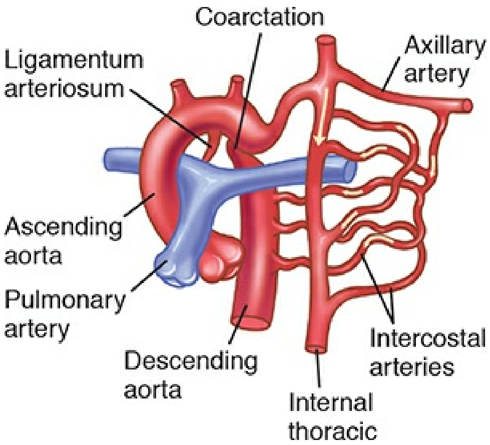


FIGURE 2.12-5. **Coarctation of the aorta, causing severe obstruction of flow to the descending thoracic aorta.** (Reproduced with permission from USMLE-Rx.com.)

History/PE

- If not detected on newborn screening, then will next present in childhood with asymptomatic hypertension (upper extremity hypertension); classic PE findings are systolic hypertension in upper extremities, low blood pressure (BP), and weak or delayed pulse (brachiofemoral delay) in lower extremities; the difference in BP between the left and right arm can indicate the point of coarctation.
- A systolic ejection or continuous murmur may be heard in the interscapular region.
- Lower extremity claudication, syncope, epistaxis, and headache may be present.

Q

A 2-year-old boy is brought to the pediatrician because of shortness of breath and easy fatigability during play. Physical examination is notable for tachypnea and a harsh 2/6 holosystolic murmur over the lower left sternal border. What is the most likely cause of the boy’s symptoms?

- In infancy, critical coarctation requires a PDA for survival. Such infants may present in the first few days of life with poor feeding, lethargy, tachypnea, and an eventual shocklike state when the PDA closes. During the newborn screening for coarctation of aorta, differential cyanosis may be seen with lower O_2 saturation in the lower extremities (postductal areas) as compared with the right arm (preductal area).

Diagnosis

- **Best initial test:** Echocardiography with Doppler color flow.
- If presenting late in childhood or young adulthood untreated, CXR will demonstrate cardiomegaly and pulmonary congestion (in infants) and rib notching of the chest (see Fig. 2.12-6A) due to enlarged intercostal arteries and the classic “3” sign (see Fig. 2.12-6B) created by aortic wall indentation with pre- and post-stenotic dilatation (in older children and adults).

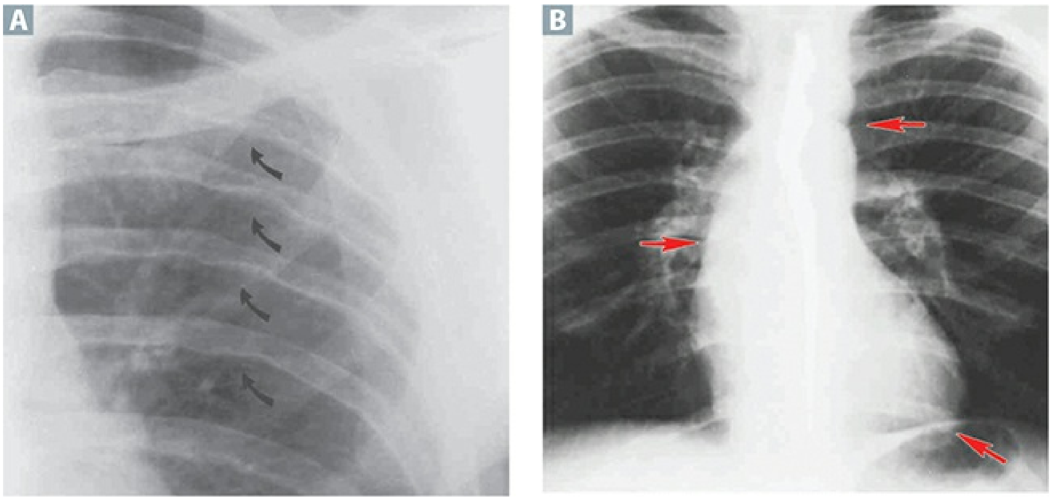


FIGURE 2.12-6. **Coarctation of the aorta. (A)** Magnified view of the left upper thorax of a patient with aortic coarctation showing multiple areas of rib notching *(arrows)*. **(B)** Posteroanterior view of another patient with aortic coarctation showing the "3 sign" of the deformed descending aorta and "E sign" on the barium-filled esophagus *(upper arrow)*. The lower arrow marks the apex of the enlarged left ventricle. The arrow on the patient's right indicates the dilated ascending aorta. (Reproduced with permission from Fuster V et al. *Hurst's The Heart,* 13th ed. New York, NY: McGraw-Hill; 2011.)

- In older children, compensatory LVH may be seen on ECG.

Treatment

- **Best initial treatment:** If severe coarctation in infancy, prostaglandin E_1 (PGE_1) to maintain ductus arteriosus patency prior to surgical repair
- Surgical repair in infants or toddlers or balloon angioplasty in older children, with or without stent placement
- Monitoring for persistent hypertension, restenosis, aneurysm development, and aortic dissection

CYANOTIC CONGENITAL HEART RIGHT-TO-LEFT SHUNTS

Patients typically present with central cyanosis soon after birth.

MNEMONIC

Cyanotic heart defects—

The five Ts that have right-to-left shunts:

Truncus arteriosus (**1** arterial vessel overriding ventricles)
Transposition of the great arteries (**2** arteries switched)
Tricuspid atresia **(3)**
Tetralogy of Fallot **(4)**
Total anomalous pulmonary venous return (**5** words)

KEY FACT

Cyanotic CHD does not respond to 100% oxygen challenge (minimal effect on Pao_2), whereas most lung pathologies will respond to 100% oxygen administration.

A

This boy probably has a large, untreated VSD that is presenting with CHF. There is less turbulence across a large defect (compared with a small one), leading to a lower-grade murmur.

TRANSPOSITION OF THE GREAT ARTERIES

Among the more common cyanotic congenital heart conditions in newborns (see Fig. 2.12-7). The aorta arises from the right ventricle (anterior), and the pulmonary trunk arises from the left ventricle (posterior) → separation of pulmonary and systemic circulations. Life is incompatible unless a shunt is present to allow mixing of blood (VSD, PDA, or patent foramen ovale). A PDA alone is usually not sufficient to allow adequate mixing of blood. Risk factors include mothers with preexisting diabetes and, rarely, DiGeorge syndrome.

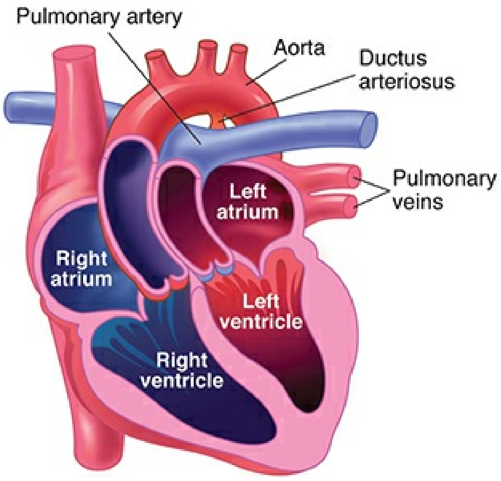


FIGURE 2.12-7. **Complete transposition of the great arteries.** Deoxygenated blood from the right ventricle is directed to the aorta, and oxygenated blood is directed back to the pulmonary artery. (Reproduced with permission from USMLE-Rx.com.)

History/PE

- Transposition of the great arteries typically presents within the first few hours after birth. It is not affected by exertion or supplemental oxygen use. Reverse differential cyanosis (higher postductal saturations than preductal saturations) may be seen if left ventricular outflow tract obstruction (eg, coarctation, aortic stenosis) is also present.
- Physical examination reveals tachypnea, progressive hypoxemia, and extreme cyanosis. Patient may have CHF, single loud S_2, and a systolic murmur (only if coexisting with VSD).

Diagnosis

- **Best initial test:** Echocardiography showing abnormal formation of the great arteries
- Classic CXR may show a heart with an “egg on a string” appearance

Treatment

- **Best initial treatment:** Intravenous PGE_1 to maintain or open the PDA
- To allow some time for growth for a more successful surgical outcome, a balloon atrial septostomy is performed to create a shunt that is not reliant on the PDA and prostaglandin infusion
- **Most definitive treatment:** Surgical correction (arterial switch operation)

TETRALOGY OF FALLOT

Consists of right ventricular outflow tract (RVOT) obstruction, overriding aorta, RVH, and VSD (see Fig. 2.12-8). Among the more common cyanotic CHDs in children. Early cyanosis results from right-to-left shunting across the VSD due to high right-sided pressures from RVOT obstruction. As right-sided pressures ↓ in the weeks after birth, the shunt direction reverses and cyanosis resolves. If the degree of pulmonary stenosis is severe, the right-sided pressures may remain high and cyanosis may persist. Risk factors include trisomy 21 and DiGeorge syndrome.

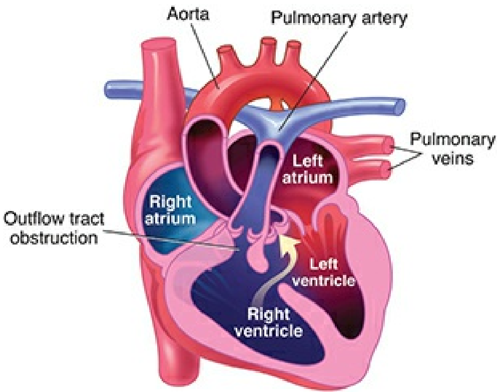


FIGURE 2.12-8. **Tetralogy of Fallot.** (Reproduced with permission from USMLE-Rx.com.)

MNEMONIC

DiGeorge syndrome—

CATCH 22

Cardiac abnormalities (TOF, VSD)
Abnormal facies (retrognathia/micrognathia, long face, short philtrum, low-set ears)
Thymic aplasia
Cleft palate
Hypocalcemia (secondary to hypoparathyroidism)
22q11 deletion

History/PE

- TOF presents in infancy or early childhood with dyspnea and fatigability. Cyanosis is frequently absent at birth but develops over the first 2 years of life; the degree of cyanosis often reflects the extent of RVOT obstruction.
- Infants are often asymptomatic until 4 to 6 months of age, when CHF may develop and manifest as diaphoresis with feeding or tachypnea.

- Children often squat for relief during hypoxemic episodes called “tet spells,” which ↑ systemic vascular resistance, thus increasing blood flow to the pulmonary vasculature and improving oxygenation.
- Hypoxemia may lead to FTT and/or cognitive or developmental delays.
- PE may reveal a systolic ejection murmur at the left upper sternal border due to pulmonic stenosis and/or a harsh holosystolic murmur at the left lower sternal border due to VSD.

KEY FACT

Both transposition of the great arteries and tetralogy of Fallot are initially treated with PGE_1 but are definitively treated with surgical correction.

Diagnosis

- **Best initial tests:** Echocardiography and catheterization.
- CXR shows a “boot-shaped” heart with ↓ pulmonary vascular markings. Remember that an isolated VSD, without RVOT, may result in ↑ pulmonary vascular markings.
- ECG shows right-axis deviation and RVH.

Treatment

- **Best initial treatment:** If there is severe RVOT obstruction or atresia, one must emergently administer PGE1 to keep the PDA open. This should be done in conjunction with surgical consultation.
- Treatment of cyanotic “tet spells” may be treated with supplemental oxygen and placing the patient in a knee-chest position. If further treatment is needed, IV fluids, opioid analgesia, β-blockers, or α-agonists can be considered, depending on the context.
- Temporary palliation can be achieved through the creation of an artificial shunt (eg, balloon atrial septotomy) before beginning the multistep surgical management (modified Blalock-Thomas-Taussig shunt is often the first step).

PEDIATRIC GASTROINTESTINAL DISEASE

PYLORIC STENOSIS

Hypertrophy of the pyloric sphincter, leading to gastric outlet obstruction. More common in first-born infant boys; can be associated with tracheoesophageal fistula, formula feeding, and maternal erythromycin ingestion.

History/PE

- Nonbilious emesis typically begins around 3 to 6 weeks of age and progresses to projectile nonbilious emesis after most or all feedings.
- Infants are hungry after episodes of vomiting; they initially feed well but eventually suffer from dehydration and malnutrition.
- PE may reveal a palpable, olive-shaped, mobile, nontender epigastric mass and visible gastric peristaltic waves.

Diagnosis

- **Best initial test:** Abdominal ultrasound will reveal a thickened, elongated pylorus (see Fig. 2.12-9).

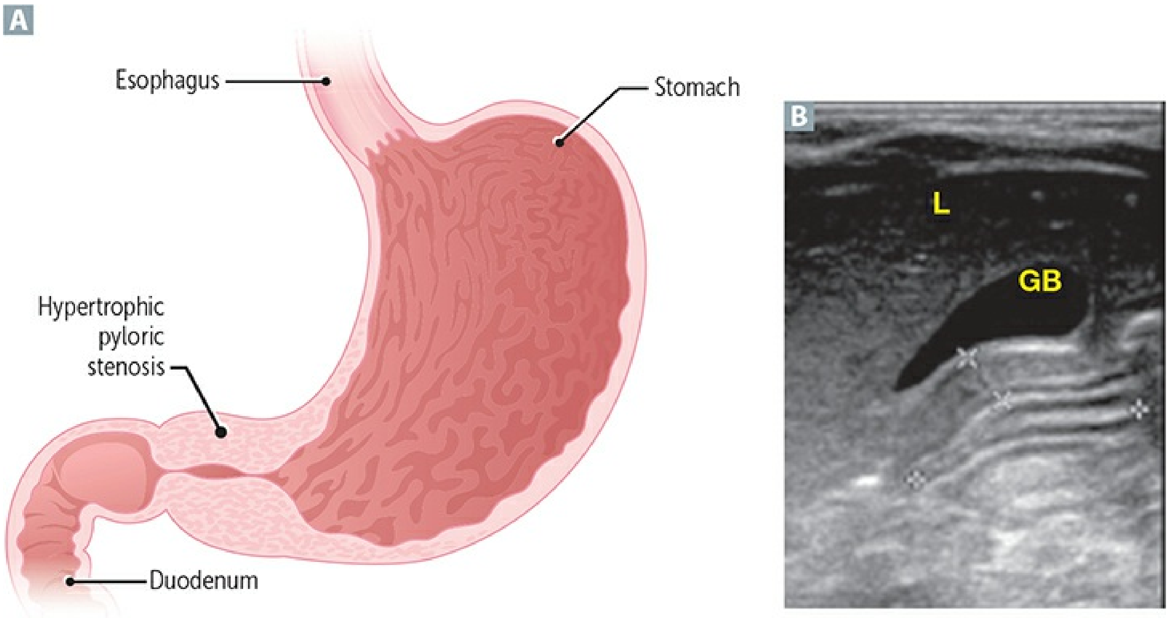


FIGURE 2.12-9. **Hypertrophic pyloric stenosis. (A)** Schematic representation of a hypertrophied pylorus. **(B)** Longitudinal ultrasound of the pylorus showing a thickened pyloric musculature *(Xs)* over a long pyloric channel length *(plus signs). GB,* Gallbladder; *L,* liver. (Reproduced with permission from USMLE-Rx.com.)

- Emesis results in loss of HCl and activation of the renin-angiotensin-aldosterone system (RAAS).
- Activation of the RAAS enhances renal K^+ and H^+ secretion in the collecting duct. The resulting lab abnormalities include hypochloremic, hypokalemic metabolic alkalosis.

Treatment

- **Best initial treatment:** Keeping the patient NPO (nothing by mouth), establishing IV access, and correcting dehydration and acid-base/electrolyte abnormalities
- **Definitive treatment:** Surgical correction with pyloromyotomy

INTUSSUSCEPTION

A condition in which a portion of the bowel invaginates, or “telescopes,” into an adjacent segment, usually proximal to the ileocecal valve (see Fig. 2.12-10). The most common cause of bowel obstruction in children between 6 months and 3 years of age (boys > girls). Etiology is unclear in most children. Risk factors include conditions with potential lead points, including Meckel diverticulum, intestinal lymphoma (>6 years of age), submucosal hematoma (as in Henoch-Schönlein purpura), polyps, and CF (lead point is inspissated stool). An antecedent viral GI illness or upper respiratory infection (URI) is seen in many children, which may cause formation of a lead point through enlargement of Peyer patches (lymphatic tissue in the bowel). There is a small risk of intussusception after the oral rotavirus vaccine.

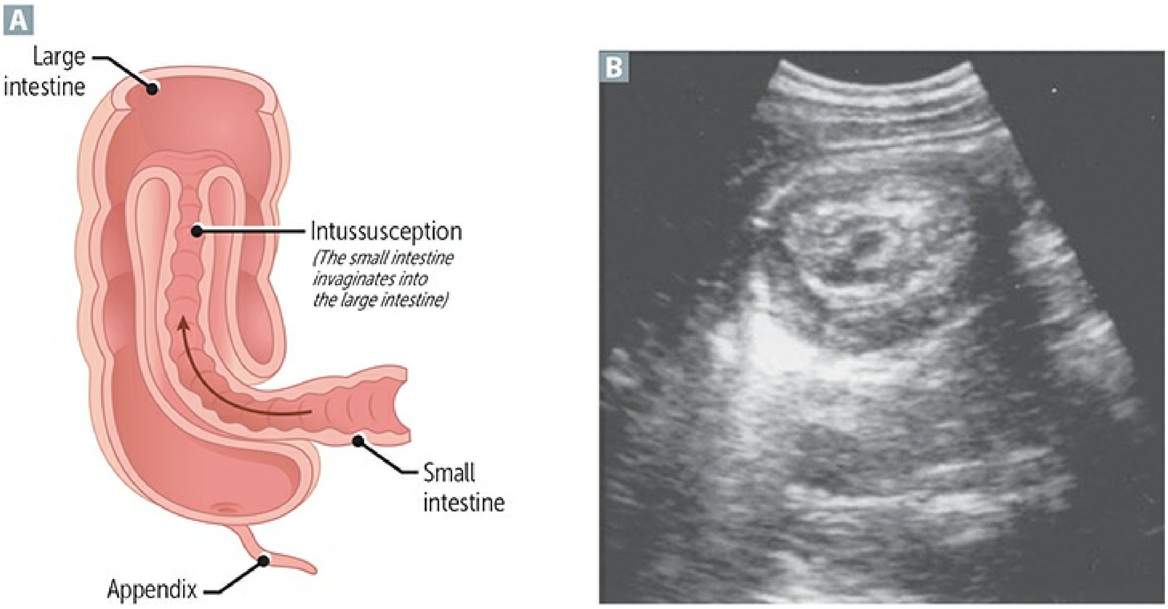


FIGURE 2.12-10. **Intussusception.** **(A)** Ileocolic intussusception, the most common location in children. **(B)** Transabdominal ultrasound showing the classic "target sign" of intussusception in cross-section. (Image A reproduced with permission from USMLE-Rx.com. Image B reproduced with permission from Ma OJ et al. Emergency Ultrasound, 2nd ed. New York, NY: McGraw-Hill; 2008.)

History/PE

- Intussusception presents with abrupt-onset, episodic abdominal pain in apparently healthy children, often accompanied by flexed knees and vomiting. The child may appear well between episodes if intussusception is released.
- The classic triad involves severe abdominal pain, vomiting (initially nonbilious and then bilious as obstruction develops), and bloody mucus in stool ("currant jelly stool," a late finding). However, this classic triad is only present in one third of patients.
- During examination, the physician should look for abdominal tenderness, a ⊕ stool guaiac test, a palpable "sausage-shaped" right upper quadrant (RUQ) abdominal mass, and "empty" right lower quadrant (RLQ) on palpation (Dance sign).

Q

A 4-week-old boy, born at term, is brought to the emergency department after experiencing vomiting of increasing frequency and intensity for the past week. His parents state that he now vomits forcefully after every meal and enthusiastically attempts to eat immediately after vomiting. The infant appears lethargic, with sunken fontanelles and decreased skin turgor. The abdomen is soft, nontender, and nondistended; no masses are felt. What is the most likely cause of this infant's symptoms?

Diagnosis/Treatment

- Ultrasonography is the initial test of choice and may show a "target sign" (see Fig. 2.12-10B). An ultrasound must be conducted during a painful episode to diagnose intussusception.
- X-rays of the abdomen are often normal early in the disease, but later they may show small bowel obstruction, perforation, or a soft tissue mass.
- The physician should correct any volume or electrolyte abnormalities, check CBC for

leukocytosis, and consider placement of a nasogastric (NG) tube for decompression.

- High clinical suspicion calls for an air insufflation enema without delay, as it is diagnostic and curative in the vast majority of patients.
- Surgical resection is indicated if the child has peritoneal signs, air insufflation enema reduction is unsuccessful, or a pathologic lead point is identified.
- Air insufflation enema is preferred over water or barium-contrast enema for diagnosis and management of intussusception, as it is faster and carries a lower risk for complications.

MALROTATION WITH VOLVULUS

Congenital malrotation of the midgut results in abnormal positioning of the small intestine (cecum in the right hypochondrium) and formation of fibrous bands known as Ladd bands (Fig. 2.12-11), which predispose to obstruction and volvulus with constriction of blood flow.

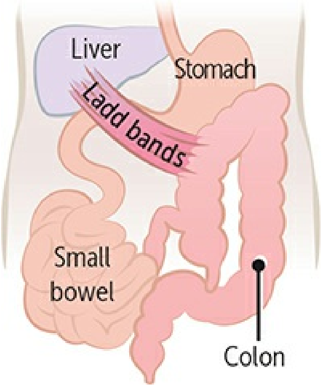


FIGURE 2.12-11. **Ladd bands.** (Reproduced with permission from USMLE-Rx.com.)

History/PE

- Often presents in the first month of life with bilious emesis, crampy abdominal pain, distention, and passage of blood or mucus in the stool.
- Postsurgical adhesions can lead to obstruction and volvulus at any point in life.

Diagnosis

- Barium contrast enema may reveal the characteristic narrowed "bird-beak" appearance and air-fluid levels, but may also appear normal.
- Upper GI series is the study of choice if the patient is stable and shows an abnormal location of the ligament of Treitz. Ultrasound may be used, but sensitivity depends on the user's experience.

Treatment

- NG tube insertion to decompress the intestine; IV fluid hydration
- Emergent surgical correction is needed when there is ischemic bowel/GI tract; definitive management is surgical (Ladd's procedure)

MECKEL DIVERTICULUM

Caused by failure of the omphalomesenteric (or vitelline) duct to obliterate, resulting in the formation of a true diverticulum containing all three layers of the small intestine (Fig. 2.12-12). Some Meckel diverticula have heterotopic gastric tissue, which places patients at risk for intestinal ulceration and painless hematochezia. This is the most common congenital abnormality of the small intestine, affecting up to 2% of children (boys > girls).

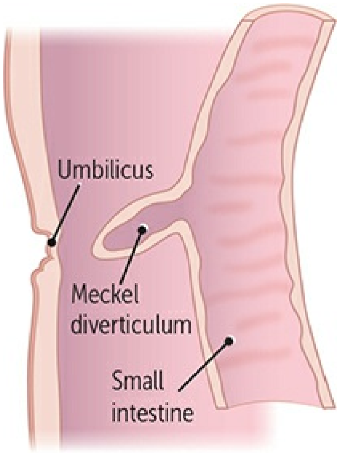


FIGURE 2.12-12. **Meckel diverticulum.** (Modified with permission from USMLE-Rx.com.)

A

This infant is most likely suffering from pyloric stenosis, an obstruction of the gastric outlet secondary to hypertrophy and hyperplasia of the muscular layers of the pylorus. Note that some infants, but not all, may present with an olive-shaped abdominal mass.

History/PE

- Typically asymptomatic and often discovered incidentally. Patients most commonly symptomatic <2 years of age.
- Classically presents with painless rectal bleeding
- Complications: Intestinal perforation or obstruction, diverticulitis (which can mimic acute appendicitis), and intussusception

MNEMONIC

Meckel rule of 2s—

Occurs in **2%** of the population
2 times more common in boys
Contains **2** types of tissue (gastric and pancreatic)
2 inches long
Found within **2** feet of the ileocecal valve

Diagnosis

- A Meckel scintigraphy scan (technetium-99m pertechnetate; detects ectopic gastric tissue) is diagnostic.
- X-rays have limited value, but can be useful in diagnosing obstruction or perforation.

KEY FACT

Bleeding is the most common complication of Meckel diverticulum; it may be minimal or severe enough to cause hemorrhagic shock.

Treatment

- **Definitive treatment:** Surgical excision of the diverticulum together with the adjacent ileal segment, which may be ulcerated
- Indications for urgent/emergent surgery include hemorrhage, diverticulitis, intestinal perforation, and obstruction/intussusception

HIRSCHSPRUNG DISEASE

Characterized by congenital lack of ganglion cells in the distal colon. This leads to decreased motility caused by unopposed smooth muscle tone in the absence of enteric relaxing reflexes and uncoordinated peristalsis (see Fig. 2.12-13). Associated with male sex, Down syndrome, Waardenburg syndrome, and multiple endocrine neoplasia type 2 (*RET* gene mutation).

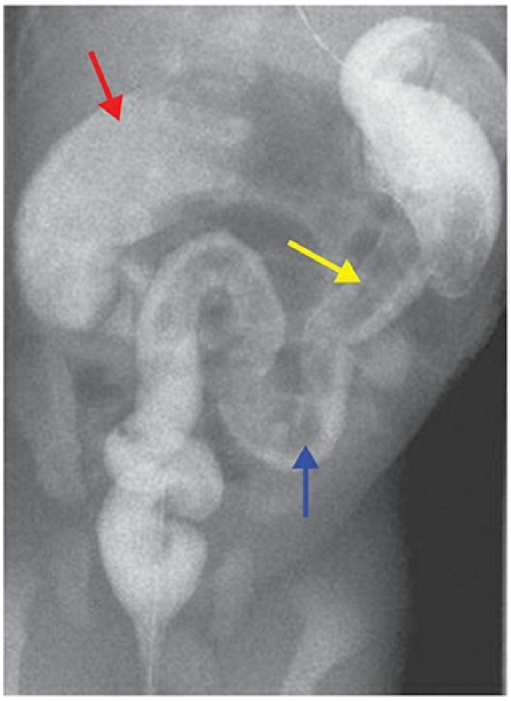


FIGURE 2.12-13. **Hirschsprung disease.** Retrograde barium enema shows small caliber of the left colon *(yellow arrow)* and rectum in comparison to the more dilated transverse colon *(red arrow).* Filling defects in the descending/sigmoid colon represent feces *(blue arrow).* (Reproduced with permission from USMLE-Rx.com.)

History/PE

- Presentation depends on the extent of the aganglionic segment.
- Neonates present with failure to pass meconium within 48 hours of birth, accompanied by bilious vomiting and FTT; children with less severe lesions may present later in life with chronic constipation.
- PE may reveal abdominal distention and explosive discharge of stool after a rectal examination; lack of stool in the rectum; and/or abnormal sphincter tone.

Diagnosis

- **Best initial test:** X-rays reveal distended bowel loops with a paucity of air in the rectum.
- Barium enema is the imaging study of choice and reveals a narrowed distal colon with proximal dilation (rectosigmoid transition zone). This test differentiates Hirschsprung disease from meconium ileus (seen in CF patients), which would show a microcolon on barium enema testing.
- Anorectal manometry detects failure of the internal sphincter to relax after distention of the rectal lumen. It is typically used in atypical presentations or older children.
- **Most accurate test**: Rectal suction biopsy confirms the diagnosis and reveals absence of the myenteric (Auerbach) plexus and submucosal (Meissner) plexus along with hypertrophied nerve trunks enhanced with acetylcholinesterase stain.

KEY FACT

Definitive diagnosis of Hirschsprung disease requires a rectal suction biopsy.

Treatment

Traditionally a two-stage surgical correction is used, involving the creation of a diverting colostomy at the time of diagnosis, followed several weeks later by a definitive “pull-through” procedure connecting the remaining colon to the rectum.

NECROTIZING ENTEROCOLITIS

A condition in which a portion of the bowel (most commonly the terminal ileum/proximal colon) undergoes necrosis. NEC is the most common GI emergency in neonates; it is most frequently seen in premature infants, but can rarely occur in full-term infants as well. Risk factors include low BW, hypotension, and enteral feeding (especially formula) in the context of a prematurity or compromised enteral blood flow.

History/PE

- Symptoms usually present within the first few days or weeks of life and are nonspecific. They include feeding intolerance, delayed gastric emptying, abdominal distention, and bloody stools.
- Symptoms can rapidly progress to intestinal perforation, peritonitis, abdominal erythema, and shock. The physician should maintain a high index of suspicion.

Diagnosis

- Lab findings are nonspecific and may show hyponatremia, metabolic (lactic) acidosis, leukopenia or leukocytosis with left shift, thrombocytopenia, and coagulopathy (disseminated intravascular coagulation [DIC] with prolonged prothrombin time/activated partial thromboplastin time [PT/aPTT] and a ⊕ D-dimer).
- X-rays of the abdomen are the imaging modality of choice and may show dilated bowel loops, pneumatosis intestinalis (“train track lucency”; see Fig. 2.12-14), portal venous gas, or abdominal free air (in the case of bowel perforation). Serial x-rays of the abdomen should be taken every 6 hours.

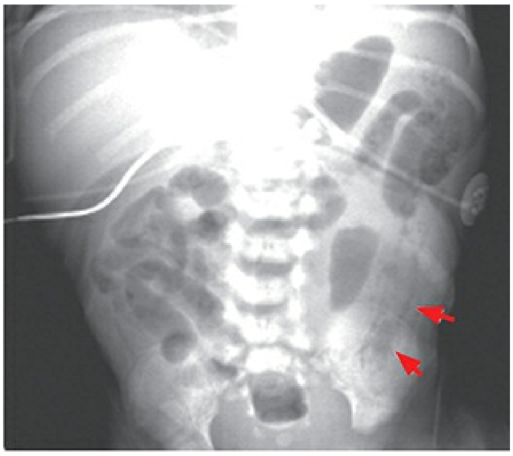


FIGURE 2.12-14. **Pneumatosis intestinalis.** Arrows highlight pneumatosis intestinalis on an abdominal x-ray of a patient with necrotizing enterocolitis. Intramural air bubbles shown in the image represent gas produced by bacteria within the bowel wall. (Reproduced with permission from Brunicardi FC et al. *Schwartz's Principles of Surgery,* 9th ed. New York, NY: McGraw-Hill; 2010.)

- Ultrasound may also be helpful in discerning free air, areas of loculation, and bowel necrosis.

KEY FACT

Pneumatosis intestinalis on x-rays is pathognomonic for NEC in neonates.

Treatment

- **Best initial treatment:** Initiate supportive measures, including NPO, an NG tube for gastric decompression, correction of dehydration and electrolyte abnormalities, total parenteral nutrition (TPN), and IV antibiotics.
- Indications for surgery are perforation (free air under the diaphragm) or worsening radiographic signs on serial abdominal x-rays. An ileostomy with mucous fistula is typically performed, with a reanastomosis at a later time.
- Complications include formation of intestinal strictures and short-bowel syndrome.

FOOD PROTEIN–INDUCED ALLERGIC PROCTOCOLITIS

Food protein–induced allergic proctocolitis (FPIAP) is a condition whereby specific food proteins (most commonly cow's milk or soy) cause inflammation of the colon via a non-IgE-mediated allergic reaction. This can occur in both breastfed and formula-fed infants and usually presents within the first few months of life.

History/PE

- Patients presents with increased volume of loose stools with mucus and painless hematochezia.
- Examination shows an afebrile, well-appearing infant, with blood- or mucus-streaked stools, and when the condition is severe, the patient may show impaired growth or failure to thrive.

Evaluation/Treatment

- Diagnosis is clinical, based on history, PE, and successful treatment. There should be notable absence of symptoms such as fever, lethargy, abdominal pain, or physical examination findings such as anal fissures or abdominal masses.
- Symptoms will resolve after removal of the antigen from the diet. In a breastfed baby, the mother has to eliminate ingestion of cow's milk, soy, or other suspected antigens. A formula-fed infant can switch to a hydrolyzed, hypoallergenic formula.

PEDIATRIC CONSTIPATION

Passage of hard stool less frequently than is appropriate for age. Bowel movements may be difficult or painful to pass. Neonates should pass meconium within 48 hours of birth. Pediatric constipation can be divided into functional and pathologic constipation. Functional constipation is responsible for 95% of cases in healthy children greater than 1 year of age.

History/PE

- Painful passage of hard, large-caliber stools or pelletlike stools. May have encopresis (involuntary leakage of soft stool around retained hard stool)
- Abdominal distention, bowel sounds hyperactive or hypoactive, depending on the underlying cause
- Stool withholding
- Associated enuresis and urinary frequency if bladder is compressed by enlarged rectum
- Palpation of hard mass of stool possible if fecal impaction occurs

Differential Diagnosis

- Functional constipation: Constipation in the absence of an anatomic abnormality or disease. Risk factors include initiation of solid food/cow's milk, periods of transition such as toilet training, and starting school.
- Hirschsprung disease: Delayed passage of meconium; may present later in childhood with chronic constipation
- CF: Inspissated meconium and chronic constipation
- Infant dyschezia: Failure to relax pelvic muscles and coordinate defecation. It presents as prolonged straining and crying with delayed passage of soft stools in an infant younger than 9 months. It resolves spontaneously with maturity.
- Spinal dysraphism and hypothyroidism.

Diagnosis

- It is important to get a thorough history regarding passage of meconium, dietary habits, onset of toilet training, and schooling.
- Organic causes of constipation should be ruled out to diagnose functional constipation. If alarm signs are present, the physician should further evaluate the patient, based on suspected etiology.
- Alarm signs include delayed passage of meconium, fever, ribbon stools, poor growth, severe abdominal distention, abnormal examination such as tuft at gluteal cleft, and increased sphincter tone.

Treatment

- The mainstay of treating pediatric constipation is prevention, including adequate fiber and water intake, as well as using a child-oriented approach to toilet training.

Q

A 4-day-old boy born at 31 weeks for intrauterine growth restriction has experienced frequent bilious vomiting after formula feeding for the past 24 hours and has passed stool mixed with bright red blood twice today. He was initially tolerating his NG feeds well, but he now demonstrates lethargy, abdominal distention, and decreased bowel sounds. What is the most likely diagnosis, and what would the physician expect to see on x-rays of the abdomen?

- Patients with episodic constipation, including stool withholding, may be treated with dietary changes and osmotic laxatives such as polyethylene glycol. Chronic functional constipation is treated with a combination of dietary changes, laxatives, and bowel retraining until laxative doses can be tapered.
- Therapies for organic constipation are targeted to the specific cause.

KEY FACT

Posterior urethral valves are the most common congenital urethral obstruction in newborn males. Classic findings are a male infant with a distended, palpable bladder; low urine output; and/or a weak urinary stream. Severe in-utero cases may lead to oligohydramnios with resultant Potter's sequence.

PEDIATRIC UROLOGY

VESICOURETERAL REFLUX

Retrograde projection of urine from the bladder to the ureters and kidneys. May be primary reflux (from abnormal/insufficient insertion of ureter into the bladder) or secondary reflux (from congenital bladder outlet obstruction, such as posterior urethral valves, or from neurogenic bladder). Classified as follows:

- **Mild reflux (grades I–II):** Reflux into one or both ureters (I) or kidneys (II) but no ureteral or renal pelvic dilation. It often resolves spontaneously.
- **Moderate to severe reflux (grades III–V):** Ureteral dilation (III), renal pelvis and calyceal dilation (IV) with associated calicyeal blunting (V) and possible nephropathy (impaired renal function in severe cases.

History/PE

May present in infancy or childhood with febrile urinary tract infections (UTIs) with particular concern for vesicoureteral reflux (VUR) if recurrent febrile UTIs. Prenatal ultrasonography may identify hydronephrosis.

Diagnosis

VCUG is diagnostic test of choice to detect abnormalities at ureteral insertion sites and to classify the grade of reflux (see Fig. 2.12-15).

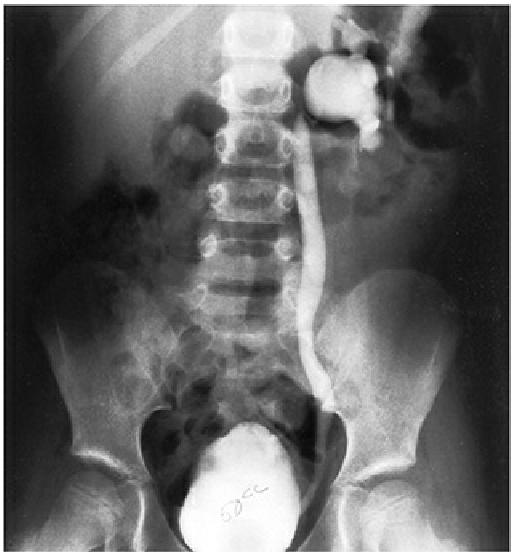


FIGURE 2.12-15. **Vesicoureteral reflux.** Frontal x-ray from a voiding cystourethrogram shows reflux to the left ureter and intrarenal collecting system with hydronephrosis. Note the absence of reflux on the normal right side. (Reproduced with permission from Doherty GM. *Current Diagnosis & Treatment: Surgery,* 13th ed. New York, NY: McGraw-Hill; 2010.)

Treatment

- The physician should have a low threshold to treat UTIs with prompt initiation of antibiotics.
- Surgery (ureteral reimplantation) is generally reserved for children with symptomatic high-grade (III–V) reflux.
- In children with recurrent febrile UTIs and VUR, daily antibiotic prophylaxis has been shown to reduce the number of febrile UTIs but not prevent renal scarring. This benefit has not been demonstrated for children with recurrent febrile UTIs without VUR.

KEY FACT

Children 2 to 24 months of age with a febrile UTI should first have an ultrasound exam to evaluate the anatomy of the urinary tract. A VCUG is indicated for recurrent febrile UTIs and abnormalities on ultrasound. For children <2 months, imaging is also recommended but evidence is limited.

A

This infant most likely has necrotizing enterocolitis, given his presentation and risk factors (prematurity, formula feeding). This is a serious diagnosis with up to 40% mortality. X-ray findings can include pneumatosis intestinalis, air in the portal venous system, and free air under the diaphragm (in case of bowel perforation).

CRYPTORCHIDISM

Failure of one or both testes to fully descend into the scrotum. Prematurity is a risk factor.

History/PE

Risk factors for cryptorchidism include prematurity, congenital urinary tract abnormalities, and certain syndromes (eg, Prader-Willi, Noonan syndromes). If not treated, it is associated with oligospermia and infertility, as well as malignancy.

Diagnosis

The testes cannot be manipulated into the scrotal sac with gentle pressure (vs retractile testes) and can be palpated anywhere along the inguinal canal.

Treatment

Orchiopexy for prepubertal boys; orchiectomy vs close observation if discovered after puberty to minimize the risk for testicular cancer. If the condition is discovered in a newborn, surgery should be performed as soon as possible after 4 months of age—imperatively before 2 years of age and ideally before 1 year of age. Earlier treatment has been found to improve fertility and decrease the risk of testicular cancer and testicular torsion.

KEY FACT

In cryptorchidism, bringing the testes into the scrotum may lower, but not eliminate, the risk for testicular cancer.

INGUINAL HERNIA

History/PE

Inguinal hernia is most commonly indirect in children. The condition has a prevalence of 1% to 5% in newborns and almost double that in premature newborns. The prevalence is three to four times higher in male newborns.

Diagnosis

- Hernia: Intermittent protrusion of abdominal contents through an abdominal wall opening. Can be either direct or indirect.
  - Direct inguinal hernia: passes medial to the epigastric vessels, behind the superficial inguinal ring and rarely enters the scrotum.
  - Indirect inguinal hernia: passes through the inguinal canal, lateral to the epigastric vessels.
- Incarceration: Entrapment of hernia that is not reducible.
- Strangulation: Ischemia and possible necrosis of the contents of the hernia, resulting in intestinal perforation.

Treatment

Reduction of the hernia and timely referral to a surgeon. Risk of incarceration and strangulation are high, especially under 1 year of age.

HYPOSPADIAS AND EPISPADIAS

Both conditions are congenital malformations of the male urethra resulting in an abnormal opening. See Table 2.12-17 and Figure 2.12-16. Immunodeficiencies can also increase susceptibility to opportunistic infections (see Figure 2.12-17.)

TABLE 2.12-17. Comparison of Hypospadias and Epispadias

PARAMETERS	HYPOSPADIAS (SEE FIG. 2.12-16 [A])	EPISPADIAS (SEE FIG. 2.12-16 [B])
Definition	Abnormal opening of penile urethra ventrally	Abnormal opening of penile urethra dorsally
Pathophysiology	Abnormality of the fusion of urethral folds	Growth of genital tubercule in the cranial instead of caudal direction
Risk factors	Low androgen levels Higher maternal age Family history Maternal exposure to environmental toxins causing hormonal disturbances	
Management	Surgical correction within first 2 years of life Circumcision should not be performed; the foreskin may be used for surgical reconstruction	

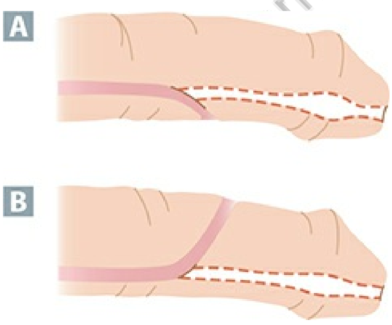


FIGURE 2.12-3. **Hypospadias (A) and epispadias (B).** (Reproduced with permission from USMLE-Rx.com.)

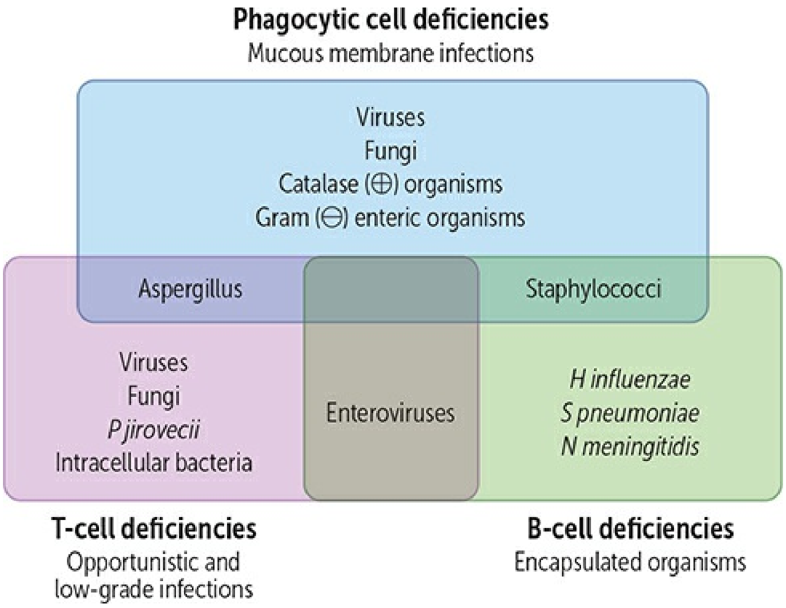

Phagocytic cell deficiencies
Mucous membrane infections
Viruses
Fungi
Catalase (⊕) organisms
Gram (⊖) enteric organisms
Aspergillus
Staphylococci
Viruses
Fungi
P jirovecii
Intracellular bacteria
Enteroviruses
H influenzae
S pneumoniae
N meningitidis
T-cell deficiencies
Opportunistic and
low-grade infections
B-cell deficiencies
Encapsulated organisms

FIGURE 2.12-17. **Infection Susceptibility According to Immune Cell Deficiency** (Reproduced

with permission from USMLE-Rx.com.)

KEY FACT

Circumcision refers to the removal of the prepuce of the penis.

- Newborn circumcision generally has fewer complications and a shorter recovery period than circumcision beyond the neonatal period.
- Circumcision has several potential benefits, eg, reduction in UTIs, STIs, and penile malignancy.
- Complications (rare) include bleeding, infection, ulceration, cosmetic issues, and stenosis.

KEY FACT

Enuresis:

- Involuntary voiding of urine.
- This can be primary, caused by immaturity of the reflex to awaken in response to a full bladder.
- Evaluation for secondary causes can become necessary (UTI, anatomic abnormality of the urinary tract).
- Treatment is not always necessary, but enuresis alarms are generally considered the first-line option in primary enuresis.

PEDIATRIC IMMUNOLOGY

IMMUNODEFICIENCY DISORDERS

Congenital immunodeficiencies are rare and often present with chronic or recurrent infections (eg, chronic thrush), unusual or opportunistic organisms, incomplete treatment response, or FTT. Categorization is based on the single immune system component that is abnormal (see Table 2.12-18).

TABLE 2.12-18. Pediatric Immune Disorders

DISORDER	DESCRIPTION	INFECTION RISK/TYPE	DIAGNOSIS/TREATMENT
B-CELL DISORDERS			
Bruton agammaglobulinemia	An X-linked recessive B-cell deficiency found only in boys Symptoms begin after 6 months of age, when maternal IgG (transferred transplacentally) diminishes in titer	Life-threatening; characterized by encapsulated *Pseudomonas, Streptococcus pneumoniae,* and *Haemophilus* infections after 6 months of age	Quantitative Ig levels: If low, confirmation with B- and T-cell subsets (B cells absent; T cells often high) Absent tonsils and other lymphoid tissue may provide a clue Treat with prophylactic antibiotics and IVIG
Common variable immunodeficiency (CVID)	Usually a combined B- and T-cell defect All Ig levels are low (in the 20s and 30s) Patient has normal B-cell numbers and ↓ plasma cells Symptoms usually present later in life (15–35 years of age)	↑ pyogenic upper and lower respiratory infections ↑ risk for lymphoma and autoimmune disease	Quantitative Ig levels; confirmation with B- and T-cell subsets Treat with IVIG
IgA deficiency	Mild; the most common immunodeficiency ↓ IgA levels only	Usually asymptomatic; possibility for patients to develop recurrent respiratory or GI infections *(Giardia)* Anaphylactic transfusion reaction caused by anti-IgA antibodies is a commonly tested presentation	Quantitative IgA levels; treatment of infections Be careful giving IVIG, as it can lead to the production of anti-IgA antibodies and cause severe allergic reactions; if IVIG is necessary, give IgA-depleted IVIG
Hyper-IgM syndrome	An X-linked recessive disease; absence of CD40 ligand that allows class-switching from IgM to other Ig classes ↑ IgM levels, low levels of all other Ig, and normal numbers of lymphocytes	Severe, recurrent sinopulmonary infections caused by impaired Ig	Treatment with antibiotic prophylaxis and IVIG
T-CELL DISORDERS			
Thymic aplasia (DiGeorge syndrome)	See the mnemonic **CATCH 22** Presents with tetany (secondary to hypocalcemia) in the first days of life Autosomal dominant	Variable risk for infection ↑↑↑ infections with viruses, fungi, and pneumocystis pneumonia (PCP) X-ray possibly showing absent thymic shadow	Absolute T-lymphocyte count; mitogen stimulation response; delayed hypersensitivity skin testing Treatment with bone marrow transplantation (BMT) and IVIG for antibody deficiency; PCP prophylaxis Thymus transplantation an alternative

DISORDER	DESCRIPTION	INFECTION RISK/TYPE	DIAGNOSIS/TREATMENT
COMBINED DISORDERS			
Ataxia-telangiectasia	Progressive cerebellar ataxia and oculocutaneous telangiectasias Caused by an autosomal-recessive mutation in the gene responsible for repair of dsDNA breaks	Triad: cerebellar defects (ataxia), spider angiomas (telangiectasia), IgA deficiency ↑ incidence of malignancies, including non-Hodgkin lymphoma, leukemia, and gastric carcinoma	No specific treatment; may require IVIG, depending on the severity of the Ig deficiency
Severe combined immunodeficiency	Most commonly X-linked recessive Severe lack of B and T cells caused by a defect in stem cell maturation and ↓ adenosine deaminase Referred to as "bubble boy disease," because children historically have been confined to an isolated, sterile environment	Severe, frequent bacterial infections; chronic candidiasis; opportunistic organisms	Treatment with bone marrow or stem cell transplantation and IVIG for antibody deficiency Requires PCP prophylaxis
Wiskott-Aldrich syndrome	An X-linked recessive disorder seen only in male patients Symptoms usually present at birth Patients have ↑ IgE/IgA, ↓ IgM, and thrombocytopenia The classic presentation involves bleeding, eczema, and recurrent otitis media Remember the mnemonic **WIPE:** **W**iskott-Aldrich, **I**nfections, **P**urpura (thrombocytopenic), **E**czema	↑↑ risk for atopic disorders, lymphoma/leukemia, and infection from *S pneumoniae*, *S. aureus*, and *H. influenzae* type b (encapsulated organisms; think back to how IgM functions)	Treatment supportive (IVIG and antibiotics) Patients are at ↑ risk for developing autoimmune diseases and malignancies Patients rarely survive to adulthood Patients with severe infections may be treated with BMT
PEDIATRIC PHAGOCYTIC DEFICIENCIES			
Chronic granulomatous disease (CGD)	An X-linked (two-thirds) or autosomal recessive (one-third) disease with deficient superoxide production by polymorphonuclear leukocytes and macrophages Anemia, lymphadenopathy, and hypergammaglobulinemia may be present	Chronic skin, lymph node, pulmonary, GI, and urinary tract infections; osteomyelitis and hepatitis Infecting organisms are catalase ⊕ (*S aureus*, *Escherichia coli*, *Candida*, *Klebsiella*, *Pseudomonas*, *Aspergillus*) Patients may have granulomas of the skin and GI/genitourinary (GU) tracts	Absolute neutrophil count with neutrophil assays The dihydrorhodamine (DHR) test is diagnostic for CGD; nitroblue tetrazolium test is the previous gold standard and still occasionally used Treat with daily trimethoprim-sulfamethoxazole (TMP-SMX); make judicious use of antibiotics during infections. Interferon (IFN)-γ can ↓ the incidence of serious infection BMT and gene therapy are new therapies

DISORDER	DESCRIPTION	INFECTION RISK/TYPE	DIAGNOSIS/TREATMENT
Leukocyte adhesion deficiency	A defect in the chemotaxis of leukocytes ↓ phagocytic activity	Recurrent skin, mucosal, and pulmonary infections Deficiency may present as omphalitis in the newborn period with delayed separation of the umbilical cord (>14 days postbirth)	No pus with minimal inflammation in wounds (caused by a chemotaxis defect) Laboratory results show leukocytosis (particularly neutrophilia) BMT is curative
Chédiak-Higashi syndrome	An autosomal recessive disorder that leads to a defect in neutrophil chemotaxis/microtubule polymerization The syndrome includes partial oculocutaneous albinism, peripheral neuropathy, and neutropenia	↑↑ incidence of overwhelming pyogenic infections with *S pyogenes*, *S aureus*, and *Pneumococcus* species	Giant granules in neutrophils BMT is the treatment of choice
Job syndrome (hyperimmunoglobulin E syndrome)	A defect in neutrophil chemotaxis Remember the mnemonic **FATED:** Coarse **F**acies **A**bscesses (*S aureus*) Retained primary **T**eeth Hyper-Ig**E** (eosinophilia) **D**ermatologic (severe eczema)	Recurrent *S aureus* infections and abscesses	Treatment with penicillinase-resistant antibiotics and IVIG
COMPLEMENT DISORDERS			
C1 esterase inhibitor deficiency (hereditary angioedema)	An autosomal dominant disorder with recurrent episodes of angioedema lasting 2–72 hours and provoked by stress or trauma	Can lead to life-threatening airway edema	Total hemolytic complement (CH50) to assess the quantity and function of complement Purified C1 inhibitor (C1INH) concentrate and fresh frozen plasma (FFP) can be used before surgery
Terminal complement deficiency (C5–C9)	Inability to form membrane attack complex	Recurrent *Neisseria* infections, meningococcal, or gonococcal Rarely, patients have lupus or glomerulonephritis	Meningococcal vaccine and appropriate antibiotics

- **B-cell deficiencies:** Most common (50%). Typically present after 6 months of age with recurrent sinopulmonary, GI infections, and/or with encapsulated organisms (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*). Treatment calls for intravenous immunoglobulin (IVIG), except for cases of IgA deficiency.
  - Bruton agammaglobulinemia can be confused with transient hypogammaglobulinemia of infancy (THI), as both are characterized by ↑ susceptibility to infections at ~6 months of age, when transplacental maternal IgG is no longer active. B cells are ↓ in Bruton, whereas those in THI are normal.
  - Bruton agammaglobulinemia and common variable immunodeficiency (CVID) also have similar symptoms. However, the former is found in boys ~6 months of age, whereas CVID is seen in older males and females (15–35 years of age), and its symptoms are less severe.
- **T-cell deficiencies:** Tend to present earlier (1–3 months of age) with opportunistic and low-grade fungal, viral, and intracellular bacterial infections (eg, mycobacteria). Secondary b-cell dysfunction can also be seen.
- **Phagocyte deficiencies:** Characterized by mucous membrane infections, abscesses, and poor wound healing. Infections with catalase ⊕ organisms (eg, *S. aureus*), fungi, and gram ⊖ enteric organisms are common.
- **Complement deficiencies:** These deficiencies are characterized by recurrent bacterial

infections with encapsulated organisms.

KEY FACT

Flashback to immunology:

- B cells make immunoglobulins and are responsible for immunity against extracellular bacteria.
- T cells are responsible for immunity against intracellular bacteria, viruses, and fungi.

KAWASAKI DISEASE

Complications: Untreated children may develop coronary artery aneurysms (25%); all patients should be assessed by echocardiography at diagnosis.

An acute multisystem medium-vessel vasculitis that primarily affects young children. Usually affects children age <5 years (↑ incidence in people of Japanese and Korean descent). Kawasaki disease is divided into acute, subacute, and convalescent phases.

MNEMONIC

Kawasaki disease symptoms—

CRASH and BURN

Conjunctivitis (without discharge)
Rash
Adenopathy (unilateral and >1.5 cm)
Strawberry tongue
Hands and feet (red, swollen, flaky skin)
BURN (fever >40°C [>104°F] for ≥5 days)

History/PE

Five days of fever and at least four of the following five criteria:

1. Conjunctivitis: Bilateral, nonexudative, painless with limbal sparing (acute phase)
2. Oral mucosal changes: Erythematous mouth/pharynx, “strawberry tongue,” and/or cracked lips (acute phase)
3. Rash: Primarily truncal, polymorphous, erythematous (acute phase)
4. Peripheral extremity changes: Edema of hands and feet, palmar erythema (acute phase), and desquamating palms and soles (convalescent phase)
5. Cervical lymphadenopathy (>1.5 cm): Generally painful and unilateral (acute phase)

Other manifestations (not required for diagnosis) include sterile pyuria, gallbladder hydrops, hepatitis, and arthritis, hyponatremia, and hypoalbuminemia

KEY FACT

Untreated Kawasaki disease can lead to coronary aneurysms in up to 25% of patients.

Diagnosis

- **Laboratory workup:** Normochromic anemia, leukocytosis with left shift, thrombocytosis, increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).
- The physician should obtain a baseline echocardiogram at diagnosis for longitudinal follow-up of coronary artery morphology. Follow-up of uncomplicated cases should occur at 2 weeks and 6 to 8 weeks after diagnosis.

KEY FACT

Kawasaki disease and scarlet fever may both present with "strawberry tongue," rash, desquamation of the hands and feet, and erythema of the mucous membranes. However, children with scarlet fever have normal lips and no conjunctivitis.

Treatment

- **Best initial treatment:** High-dose aspirin (acetylsalicylic acid [ASA]), for anti-inflammatory, antipyretic, and antithrombotic effects and IVIG to reduce the risk of coronary artery aneurysms from 25% to <5%.
- Low-dose ASA is then continued until normalization of laboratory inflammatory markers. Aspirin is continued if children develop coronary aneurysms. Although young children taking ASA are at risk for Reye syndrome, the risk/benefit favors treatment with ASA to prevent coronary artery aneurysms.
- Corticosteroids may be used in IVIG-refractory cases, but routine use is not recommended.

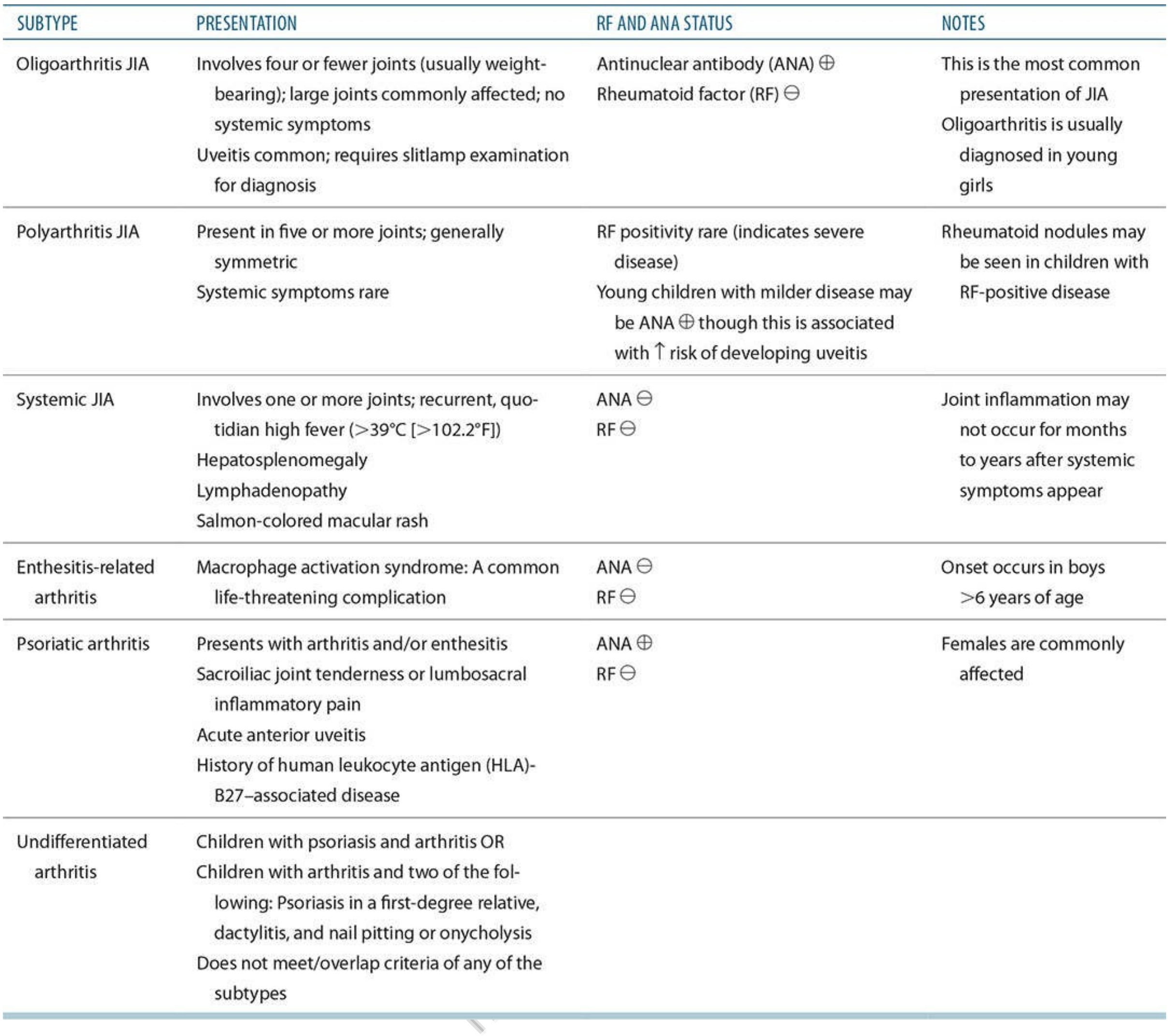
KEY FACT

ASA is used for Kawasaki disease in the pediatric population, despite fear of Reye syndrome, a rare but serious condition. Although the exact mechanism is unclear, Reye syndrome results from mitochondrial injury and fatty degenerative liver failure, which leads to hyperammonemia and ultimately encephalopathy.

JUVENILE IDIOPATHIC ARTHRITIS

An autoimmune disorder manifesting as arthritis with "morning stiffness" and gradual loss of motion that is present for at least 6 weeks in a patient <16 years of age. Formerly known as juvenile rheumatoid arthritis (JRA). Approximately 95% of cases are resolved by puberty. This disorder is more common in girls than in boys. The most common clinical and laboratory findings of different subtypes of juvenile idiopathic arthritis (JIA) are described in Table 2.12-19.

TABLE 2.12-19. **Juvenile Idiopathic Arthritis Subtypes**



SUBTYPE	PRESENTATION	RF AND ANA STATUS	NOTES
Oligoarthritis JIA	Involves four or fewer joints (usually weight-bearing); large joints commonly affected; no systemic symptoms Uveitis common; requires slitlamp examination for diagnosis	Antinuclear antibody (ANA) ⊕ Rheumatoid factor (RF) ⊖	This is the most common presentation of JIA Oligoarthritis is usually diagnosed in young girls
Polyarthritis JIA	Present in five or more joints; generally symmetric Systemic symptoms rare	RF positivity rare (indicates severe disease) Young children with milder disease may be ANA ⊕ though this is associated with ↑ risk of developing uveitis	Rheumatoid nodules may be seen in children with RF-positive disease
Systemic JIA	Involves one or more joints; recurrent, quotidian high fever (>39°C [>102.2°F]) Hepatosplenomegaly Lymphadenopathy Salmon-colored macular rash	ANA ⊖ RF ⊖	Joint inflammation may not occur for months to years after systemic symptoms appear
Enthesitis-related arthritis	Macrophage activation syndrome: A common life-threatening complication	ANA ⊖ RF ⊖	Onset occurs in boys >6 years of age
Psoriatic arthritis	Presents with arthritis and/or enthesitis Sacroiliac joint tenderness or lumbosacral inflammatory pain Acute anterior uveitis History of human leukocyte antigen (HLA)-B27–associated disease	ANA ⊕ RF ⊖	Females are commonly affected
Undifferentiated arthritis	Children with psoriasis and arthritis OR Children with arthritis and two of the following: Psoriasis in a first-degree relative, dactylitis, and nail pitting or onycholysis Does not meet/overlap criteria of any of the subtypes		

Diagnosis

See Table 2.12-19.

Q

A 2-year-old boy is brought to the pediatrician for a skin infection that started on his chin and rapidly spread to involve much of his face and neck. This is his third such infection this year, and he is constantly plagued by sinus infections and bouts of pneumonia. There is no family history of recurrent infections. The patient appears uncomfortable, and dermatologic exam is notable for erosions coated in yellow crust that are widespread across the patient's face and neck. He also has patchy white pigmentation of the skin, light blonde hair, and blue eyes. What is the most likely diagnosis?

Treatment

- **Best initial treatments:** NSAIDs and strengthening exercises
- Corticosteroids (for myocarditis) and immunosuppressive medications (methotrexate, anti–tumor necrosis factor agents such as etanercept) are second-line agents

PEDIATRIC INFECTIOUS DISEASE

ACUTE OTITIS MEDIA

A suppurative infection of the middle ear cavity that is common in children. Sixty percent of children will develop one or more episodes of AOM before 4 years of age. Common pathogens include *S pneumoniae;* nontypeable *H influenzae; Moraxella catarrhalis;* and viruses such as influenza A, respiratory syncytial virus (RSV), and parainfluenza virus.

History/PE

Symptoms include ear pain, fever, crying, irritability, difficulty feeding or sleeping, vomiting, and diarrhea. Young children may tug on their ears.

Risk Factors

- Family history, day care, and tobacco smoke and air pollution exposure. Rate peaks between 6 and 12 months of age.
- Protective factors: Breastfeeding, oral xylitol.

Diagnosis

Diagnosis is made clinically.

- Otoscopic examination reveals an erythematous tympanic membrane (TM) effusion, bulging, or retraction of the TM and ↓ TM mobility (test with an insufflator bulb). Viral causes may result in serous otitis media with blue-gray bulging membranes.
- Serous otitis media is the presence of effusion without active infection. Examination shows a dull TM.

Treatment

- **Best initial treatment:** For mild cases of unilateral otitis media in children >6 months of age, treatment options include supportive care (pain and fever control) and close follow-up rather than antibiotics.
- If antibiotics are used, the physician can prescribe high-dose amoxicillin (80–90 mg/kg/day) for 10 days for empiric therapy. Patients with recent amoxicillin use and those with resistant or recurrent cases may require amoxicillin/clavulanic acid. If patient is allergic to penicillin, the physician can consider cephalosporin (mild delayed reaction) or azithromycin (immediate serious or delayed reaction).
- Complications include TM perforation, mastoiditis, meningitis, cholesteatomas, and chronic otitis media. Recurrent otitis media can cause hearing loss with resultant speech and language delay. Chronic otitis media may require tympanostomy tubes.

A

This child most likely has Chédiak-Higashi syndrome, caused by autosomal recessive defects in the synthesis/maintenance of storage granules in a number of cell types (including leukocytes, platelets, neutrophils, and melanocytes). In addition to partial oculocutaneous albinism, these patients experience hepatosplenomegaly and recurrent, serious infections of the skin and respiratory tract by *S aureus*, *Streptococcus pyogenes,* and

Pneumococcus species. Chédiak-Higashi syndrome is often fatal in childhood because of overwhelming infection.

BRONCHIOLITIS

An acute inflammatory illness of the small airways of the lower respiratory tract that primarily affects infants and children <2 years of age, often in the fall or winter. RSV is the most common cause; others include parainfluenza, influenza, metapneumovirus, and other viruses. Progression to respiratory failure is a potentially fatal complication. Risk factors for severe RSV infection include <6 months of age, prematurity, heart or lung disease, neuromuscular disease, and immunodeficiency.

KEY FACT

Toddlers and older infants are at risk for foreign body aspiration. Sudden-onset wheezing or respiratory distress are often characteristic. Objects that cause airway compromise or that cause mucosal damage (batteries) should be removed immediately with bronchoscopy.

History/PE

- **Presentation:**
  - **Days 1 to 3:** Low-grade fever, rhinorrhea, cough. Young infants might have apnea. This is believed to be due to impaired central respiratory center function in the setting of the stress of infection.
  - **Days 4 to 6:** Respiratory distress, tachypnea, hypoxia.
- **PE:** Tachypnea, hypoxia, intercostal retractions, crackles or coarse breath sounds ("washing machine sounds"), ± wheezing
- An ↑ respiratory rate: Earliest and most sensitive vital sign change

KEY FACT

RSV is the most common cause of bronchiolitis. Parainfluenza is the most common cause of croup.

Diagnosis

- Bronchiolitis is predominantly a clinical diagnosis. Routine cases do not need any laboratory or radiologic workup.
- In severe cases, a CXR can be obtained to rule out pneumonia. The x-ray may show hyperinflation of the lungs with a flattened diaphragm, interstitial infiltrates, and/or atelectasis.
- Nasopharyngeal aspirate to test for RSV and other viruses is highly sensitive and specific but has little effect on management (infants should be treated for bronchiolitis whether or not a virus is identified).

KEY FACT

Young infants are at risk for apnea as a result of RSV bronchiolitis.

Treatment

- Treatment for bronchiolitis is primarily supportive with hydration, suctioning, and supplemental O_2.
- For patients with a history or strong family history of asthma, treatment with bronchodilators may be considered, and if symptoms improve, may be continued.
- Hospitalization of patient is necessary if infant's hypoxia and/or tachypnea interfere with feeding or if signs of severe illness are present.
- Corticosteroids are not indicated.
- Ribavirin is an antiviral drug sometimes used in high-risk infants with underlying heart, lung, or immune disease. The American Academy of Pediatrics recommends against the use of ribavirin in otherwise healthy children.
- RSV prophylaxis with injectable monoclonal antibodies (palivizumab) is recommended in the fall/winter for high-risk patients ≤2 years of age (eg, those with a history of prematurity, chronic lung disease, or CHD).

CROUP (LARYNGOTRACHEOBRONCHITIS)

An acute viral inflammatory disease of the larynx, primarily within the subglottic space. Pathogens include parainfluenza virus types 1 (most common), 2, and 3; RSV; influenza; and adenovirus. Rarely, bacterial superinfection may develop, causing tracheitis.

History/PE

Prodromal URI symptoms are typically followed by low-grade fever, mild dyspnea, inspiratory stridor that worsens with agitation, a hoarse voice, and a characteristic barking cough that worsens at night.

Diagnosis

- Croup is diagnosed by clinical impression. The diagnosis is often based on the degree of stridor and respiratory distress.
- An anteroposterior x-ray of the neck may show the classic "steeple sign" from subglottic narrowing (see Fig. 2.12-18), but this finding is neither sensitive nor specific.

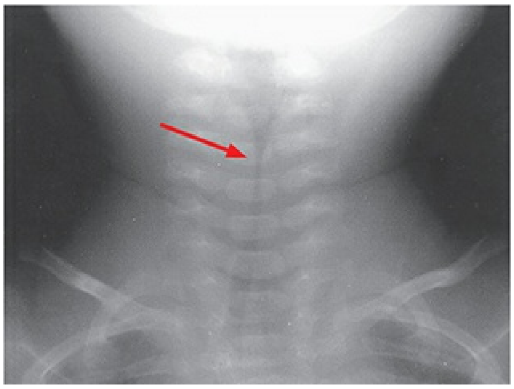


FIGURE 2.12-18. Croup. Anteroposterior x-ray of the neck in this 1-year-old child with inspiratory stridor and cough shows the classic "steeple sign" *(arrow)* consistent with the subglottic narrowing of laryngotracheobronchitis. (Reproduced with permission from Stone CK, Humphries RL. *Current Diagnosis & Treatment: Emergency Medicine*, 6th ed. New York, NY: McGraw-Hill; 2008.)

- Table 2.12-20 and Figure 2.12-19 differentiate croup from epiglottitis and tracheitis.

TABLE 2.12-20. Characteristics of Croup, Epiglottitis, and Tracheitis

VARIABLE	CROUP (MOST COMMON)	EPIGLOTTITIS	TRACHEITIS
Age group affected	3 months to 3 years	3–7 years	3 months to 2 years
Anatomic structures affected (see Fig.2.12-19).	Larynx Subglottic airway	Epiglottis Aryepiglottic folds	Trachea
Pathogen	Parainfluenza virus	*H influenzae type B, S pneumoniae*	Often *S aureus;* follows viral URI
Onset	Prodrome (1–7 days)	Rapid (4–12 hours)	Prodrome (3 days) leading to acute decompensation (10 hours)
Fever severity	Low grade and often afebrile	High grade	High grade
Associated symptoms	Barking cough, inspiratory stridor, hoarseness	Respiratory distress: Acute decompensation, toxic appearance, inspiratory stridor, muffled voice, drooling, tripoding	Acute and severe respiratory distress but slower onset than epiglottitis; presence of pseudomembranes or purulent secretions on examination
Response to racemic epinephrine	Stridor improves	None	None
Findings on x-ray of neck	"Steeple sign" on anteroposterior x-ray	"Thumbprint sign" on lateral film	Subglottic narrowing in anteroposterior x-ray

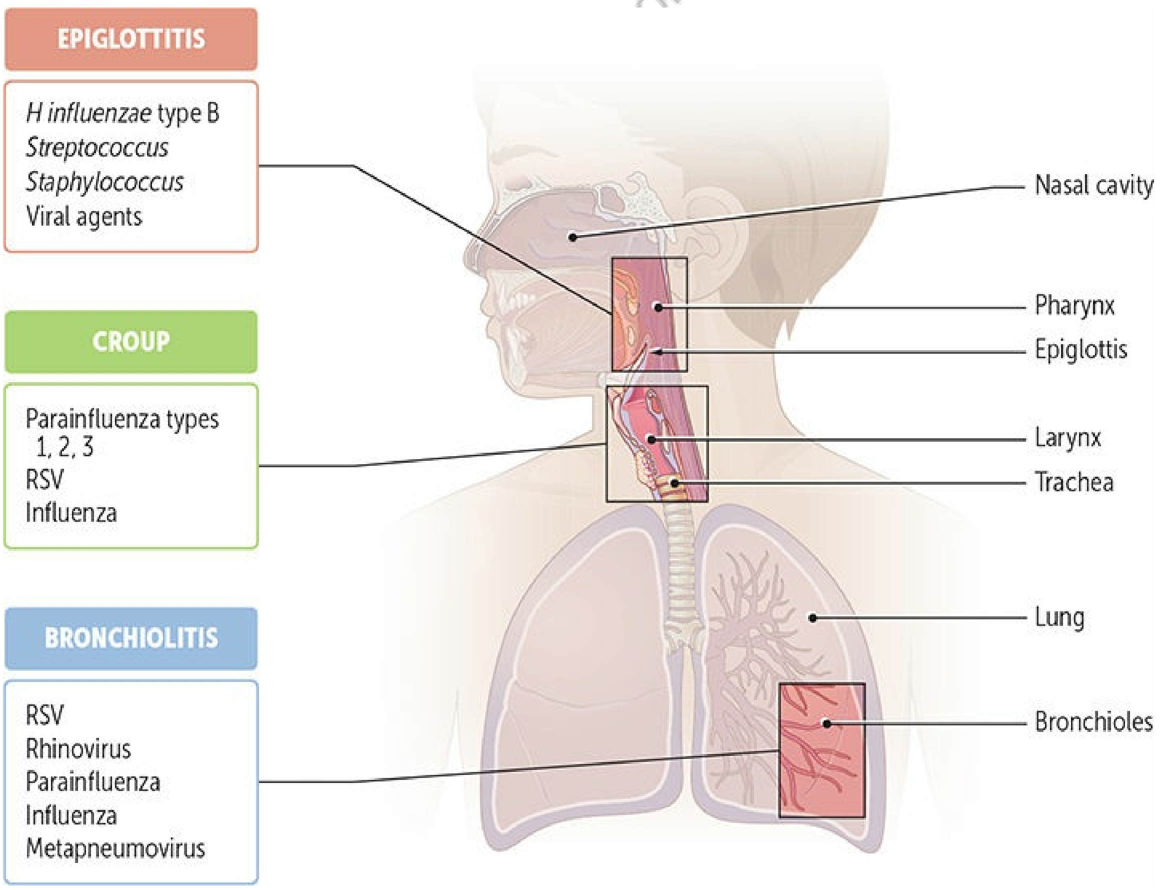

EPIGLOTTITIS
H influenzae type B
Streptococcus
Staphylococcus
Viral agents
CROUP
Parainfluenza types 1, 2, 3
RSV
Influenza
BRONCHIOLITIS
RSV
Rhinovirus
Parainfluenza
Influenza
Metapneumovirus
Nasal cavity
Pharynx
Epiglottis
Larynx
Trachea
Lung
Bronchioles

FIGURE 2.12-19. **Epiglottis, croup, and bronchiolitis: Anatomy.** (Reproduced with permission from USMLE-Rx.com.)

Treatment

- **Mild cases:** Outpatient management with cool-mist therapy and fluids
- **Moderate cases:** May require supplemental O_2, oral or intramuscular (IM) corticosteroids, and nebulized racemic epinephrine
- **Severe cases** (eg, respiratory distress at rest, inspiratory stridor, accessory neck muscle use): Hospitalization and nebulized racemic epinephrine. The physician should consider intubation if there is danger of airway compromise.

EPIGLOTTITIS

A serious and rapidly progressive infection of supraglottic structures (eg, the epiglottis and aryepiglottic folds). Before immunization, *H influenzae* type b was the primary pathogen. Common causes now include *Streptococcus* species, nontypeable *H influenzae,* and viral agents, but this is now a very rare infection in the postvaccine era.

History/PE

- Epiglottitis presents with acute-onset high fever (39–40°C [102–104°F]), dysphagia, drooling, a muffled voice, inspiratory retractions, cyanosis, and soft stridor.
- Patients sit with the neck hyperextended and the chin protruding (“sniffing dog” position) and lean forward in a “tripod” position to maximize air entry.
- Untreated infection can rapidly lead to life-threatening airway obstruction and respiratory arrest.

Diagnosis

- Epiglottitis is diagnosed by clinical impression. The differential diagnosis must include diffuse and localized causes of airway obstruction (see Table 2.12-21).

TABLE 2.12-21. **Additional Differential Diagnosis of Epiglottitis: Retropharyngeal vs Peritonsillar Abscess**

VARIABLE	RETROPHARYNGEAL ABSCESS	PERITONSILLAR ABSCESS
Age group affected	From 6 months to 6 years of age	Usually >10 years of age
History/PE	Acute-onset high fever with sore throat, a muffled “hot potato” voice, trismus, drooling, and cervical lymphadenopathy Presentation is usually unilateral; a mass may be seen in the posterior pharyngeal wall on visual inspection	Sore throat, a muffled “hot potato” voice, trismus, drooling, uvula displaced to opposite side
Pathogen	Group A streptococcus (most common), *S aureus, Bacteroides;* often polymicrobial in origin	Group A streptococcus (most common), *S aureus, S pneumoniae,* anaerobes
Preferred position	Sitting up or flexion of neck (supine position with the neck extended worsens symptoms)	None
Diagnosis	On lateral x-ray of the neck, soft tissue plane should be ≤50% of the width of the corresponding vertebral body Contrast CT of the neck helps differentiate abscess from phlegmon (soft tissue infection)	Usually clinical
Treatment	Aspiration or incision and drainage of abscess; antibiotics	Incision and drainage ± tonsillectomy; antibiotics

- The airway must be secured before a definitive diagnosis can be made. In light of potential laryngospasm and airway compromise, an examination of the throat should only be done in the presence of an anesthesiologist or otolaryngologist.

- Definitive diagnosis is made via direct fiberoptic visualization of cherry-red, swollen epiglottis and arytenoids.
- Lateral x-ray shows a swollen epiglottis obliterating the valleculae ("thumbprint sign"; see Fig. 2.12-20).

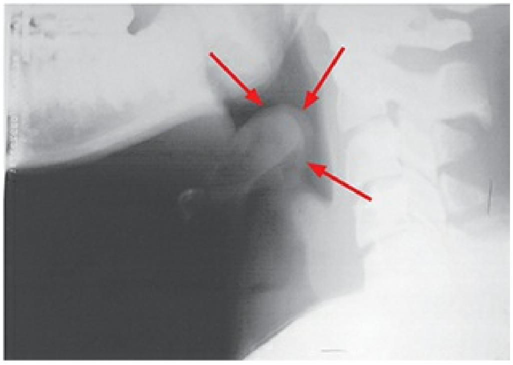


FIGURE 2.12-20. **Epiglottitis.** Lateral x-ray of the neck shows a markedly swollen epiglottis *(arrows)* demonstrating the classic "thumbprint sign," with near-complete airway obstruction. (Reproduced with permission from Stone CK, Humphries RL. *Current Diagnosis & Treatment: Emergency Medicine,* 6th ed. New York, NY: McGraw-Hill; 2008.)

Treatment

Remember the ABCs. Secure the airway first with endotracheal intubation or tracheostomy and then give IV antibiotics (ceftriaxone or cefuroxime).

KEY FACT

Epiglottitis is a true emergency and can lead to life-threatening airway obstruction. Time should not be wasted on ordering an x-ray.

MENINGITIS

Bacterial meningitis most often occurs in children <3 years of age; common organisms include *S pneumoniae, N meningitidis,* and *Escherichia coli.* Enteroviruses are the most common agents of viral meningitis, and they infect children of all ages. Risk factors for bacterial meningitis include sinofacial infections, trauma, immunodeficiency, and sepsis.

Most common causes of bacterial meningitis by age are as follows:

- **Neonates:** Group B *Streptococcus* (GBS), *E coli, Listeria*
- **Infants/children:** *S pneumoniae, N meningitidis, H influenzae*
- **Adolescents:** *N meningitidis, S pneumoniae*

History/PE

- Bacterial meningitis in older children classically presents with the triad of headache, high fever, and nuchal rigidity. Infants can present with fever and irritability.
- Viral meningitis is typically preceded by a prodromal illness that includes fever, upper respiratory symptoms, and fatigue.

- Kernig sign (reluctance of knee extension when the hip is flexed) and Brudzinski sign (hips are flexed in response to forced flexion of the neck) are nonspecific signs of meningeal irritation in older children, but not in infants.
- Additional PE findings may include signs of ↑ intracranial pressure ([ICP] papilledema, cranial nerve palsies) or a petechial rash (*N meningitidis*). Signs in neonates include lethargy, hyperthermia or hypothermia, poor tone, a bulging fontanelle, and vomiting.

KEY FACT

Don't be fooled—infants rarely have meningeal signs such as Kernig or Brudzinski signs or nuchal rigidity because of their open fontanelle, which helps relieve the increased ICP.

Diagnosis

- The physician should obtain a CT scan of the head to rule out ↑ ICP (risk for brainstem herniation) if the patient is at high risk (eg, exhibits neurologic deficits or has papilledema on funduscopic exam); however, this is not typically needed in infants because the open fontanelle makes an increase of ICP less of an issue.
- The physician should arrange for a lumbar puncture (LP) and send diagnostic testing, including cell count with differential, glucose and protein levels, Gram stain, and culture.
- In bacterial meningitis, findings include high WBC, low glucose, high protein, ⊕ Gram stain, and ⊕ culture.
- In viral meningitis, the patient may just have a high WBC level with normal to high protein.

Treatment

- Treat neonates with ampicillin and cefotaxime or gentamicin. Consider acyclovir if there is concern for herpes encephalitis (eg, if the mother had herpes simplex virus [HSV] lesions at the time of the infant's birth or if the infant has an extremely bloody, nontraumatic LP).
- Give older children ceftriaxone and vancomycin.

KEY FACT

Neonates should not be given ceftriaxone in light of the ↑ risk for biliary sludging and kernicterus.

OCULAR INFECTIONS OF THE NEONATE

Infectious conjunctivitis is transmitted as the neonate passes through the birth canal during labor, and the infection often presents during the first weeks of life. The most common causative agents include *Chlamydia trachomatis* and HSV (usually HSV-2). *Neisseria gonorrhoeae* was much more common before the routine use of prophylaxis. Now it causes <1% of cases of neonatal conjunctivitis in the United States. Erythromycin ointment is recommended as first-line prophylaxis. Silver nitrate is more effective for penicillinase-productive *N gonorrhoeae.*

History/PE

Table 2.12-22 summarizes the clinical presentation of common neonatal ocular infections.

TABLE 2.12-22. **Ocular Infections in the Neonatal Period**

CAUSATIVE AGENT	CHARACTERISTICS	TREATMENT
Chlamydia trachomatis	Symptoms appear 1–2 weeks after birth Presents with eyelid swelling and relatively scant watery discharge	Topical erythromycin ointment and oral erythromycin Topical antibiotics alone are insufficient, as systemic infection is often present
Neisseria gonorrhoeae	Symptoms appear within 1 week of birth Bilateral purulent conjunctivitis and marked eyelid edema Tends to be more severe than chlamydial conjunctivitis	IV/IM third-generation cephalosporin Gonococcal coverage is crucial if the causative agent is unknown, as corneal ulceration (and resultant scarring) can occur within 24–48 hours
Herpes simplex virus	Symptoms appear within 2 weeks of birth Presents with conjunctival injection, watery/serosanguineous eye discharge, and vesicular eruptions surrounding the eyes	IV acyclovir for 14- to 21-day course, along with a topical agent (such as vidarabine)

Diagnosis

- Bacterial cultures and Gram stain represent the gold standard for suspected gonococcal or chlamydial conjunctivitis.
- HSV polymerase chain reaction (PCR) is the diagnostic standard for children with corneal ulceration or for those with a vesicular eruption anywhere on the body.
- The neonate’s mother should undergo cervical Gram stain and culture if a sexually transmitted infection is the suspected cause of conjunctivitis.

Treatment

- Empiric treatment can start before culture results are known.
- Specific treatments are listed in Table 2.12-22.

PERTUSSIS (WHOOPING COUGH)

A highly infectious form of bronchitis caused by the encapsulated gram ⊖ bacillus *Bordetella pertussis*. The diphtheria, tetanus, acellular pertussis (DTAP) vaccine (given in five doses in early childhood) is protective, but immunity wanes by adolescence, and so booster vaccination is recommended every 10 years. Adolescents and young adults serve as the primary reservoir for pertussis; a physician should not exclude it as a diagnosis in young adults with paroxysms of cough. Transmission is through aerosol droplets and requires airborne precautions with a mask. Pertussis can be life-threatening for young infants but is generally a milder infection in older children and adults.

History/PE

- Has the following three stages:
  - Catarrhal (mild URI symptoms; lasts 1–2 weeks)
  - Paroxysmal (paroxysms of cough with inspiratory whoop and post-tussive emesis; lasts 2–3 months)
  - Convalescent (symptoms wane)
- Patients most often present in the paroxysmal stage, but are most contagious in the catarrhal stage

KEY FACT

The classic presentation of pertussis is an infant <6 months of age with paroxysmal coughing, post-tussive emesis, and apnea. The typical "whooping" cough is usually absent at this age.

Diagnosis

- Labs show an elevated WBC count with lymphocytosis (often ≥70%)
- **Most accurate test:** Nasopharyngeal culture or PCR

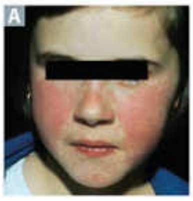
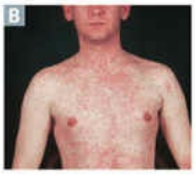
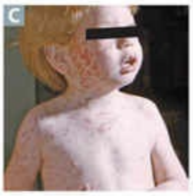
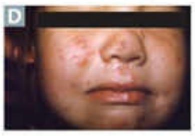
Treatment

- Hospitalize infants <6 months of age.
- Give azithromycin for 10 days to patients. Exposed newborns are at high risk irrespective of their immunization status because they may not be entirely protected by maternal transplacental immunoglobulins.
- Close contacts (including day care contacts) should receive prophylactic antibiotics (azithromycin for 5 days).

VIRAL EXANTHEMS

Table 2.12-23 outlines the clinical presentation of common viral exanthems.

TABLE 2.12-23. **Viral Exanthems**

DISEASE	CAUSE	SYMPTOMS	COMPLICATIONS
Erythema infectiosum (fifth disease) 	Parvovirus B19	Prodrome: None; fever often absent or low grade Rash: "Slapped-cheek," pruritic, maculopapular, erythematous rash (see Image A); rash starts on the arms and spreads to the trunk and legs; rash worsens with fever and sun exposure	Arthropathy in children and adults Congenital infection is associated with fetal hydrops and death Aplastic crisis may be precipitated in children with ↑ RBC turnover (eg, sickle cell anemia, hereditary spherocytosis) or in those with ↓ RBC production (eg, severe iron-deficiency anemia)
Measles 	Paramyxovirus	Prodrome: Fever (can be as high as 40°C [104°F]) with **C**ough, **C**oryza, and **C**onjunctivitis (the **"3 Cs"**); Koplik spots (small irregular red spots with central gray specks) appear on the buccal mucosa after 1–2 days Rash: An erythematous maculopapular rash that spreads from head to toe (see Image B) Treatment with vitamin A may improve symptoms	Common: Otitis media, pneumonia, laryngotracheitis Rare: Subacute sclerosing panencephalitis Airborne infectious precautions are needed because of high level of contagiousness
Rubella ("3-day measles") 	Rubella virus	Prodrome: Asymptomatic or tender, generalized lymphadenopathy (clue: posterior auricular lymphadenopathy) Rash: An erythematous, tender maculopapular rash that also spreads from head to toe (see Image C) In contrast to measles, children with rubella often have only a low-grade fever and do not appear as ill Polyarthritis may be seen in adolescents	Encephalitis, thrombocytopenia (a rare complication of postnatal infection) Congenital infection is associated with congenital anomalies (PDA, deafness, cataracts, intellectual disabilities)
Roseola infantum	Human herpes virus (HHV)-6 and HHV-7	Prodrome: Acute onset of high fever (>40°C [>104°F]); no other symptoms for 3–4 days Rash: A maculopapular rash that appears as fever breaks (begins on the trunk and quickly spreads to the face and extremities) and often lasts <24 hours	Febrile seizures that may result from rapid fever onset
Varicella (chickenpox) 	Varicella-zoster virus (VZV)	Prodrome: Mild fever, anorexia, and malaise that precede the rash by 24 hours Rash: Generalized, pruritic, "teardrop" vesicles on red base; lesions are often at different stages of healing (see Image D); rash usually appears on the face and spreads to the rest of the body, sparing the palms and soles Infectious from 24 hours before eruption until lesions crust over	Progressive varicella with meningoencephalitis, pneumonia, and hepatitis in the immunocompromised Skin lesions may develop secondary bacterial infections Reye syndrome may occur if a child takes aspirin to address the fever Varicella may be prevented with vaccine or with postexposure prophylaxis for nonimmunized patients >1 year of age (immunoglobulin for the immunocompromised and vaccine for the immunocompetent)

DISEASE	CAUSE	SYMPTOMS	COMPLICATIONS
Varicella zoster	VZV	Prodrome: Reactivation of varicella infection; disease starts as pain along an affected sensory nerve Rash: Pruritic "teardrop" vesicular rash in a dermatomal distribution; rash is uncommon unless the patient is immunocompromised	Encephalopathy, aseptic meningitis, pneumonitis, thrombotic thrombocytopenic purpura (TTP), Guillain-Barré syndrome, cellulitis, arthritis
Hand-foot-and-mouth disease	Coxsackie A	Prodrome: Fever, anorexia, oral and throat pain Rash: Oral ulcers; maculopapular vesicular rash on the hands and feet and sometimes on the buttocks	Aseptic meningitis, encephalitis, pneumonia, myopericarditis

Image A reproduced with permission from Wolff K, Johnson RA. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology,* 6th ed. New York: McGraw-Hill; 2009. Image B reproduced with permission from Wolff K, et al. *Fitzpatrick's Dermatology in General Medicine,* 7th ed. New York: McGraw-Hill; 2008. Image C adapted with permission from the Centers for Disease Control and Prevention. Image D reproduced with permission from the Centers for Disease Control and Prevention and Dr John Noble, Jr.

TORCH INFECTIONS

Refer to the Obstetrics chapter.

PINWORM INFECTION

Caused by *Enterobius vermicularis*. Pinworm is a parasitic infection that causes perianal pruritus, which is more pronounced at night. Diagnosis is made with the tape test (clear tape is pressed to the anal region in the morning and observed under the microscope for pinworm eggs). The patient and all household contacts should be treated with albendazole or pyrantel pamoate.

NEONATAL FEVER (<28 DAYS OLD)

- Fever is defined as a rectal temperature ≥38°C (≥100.4°F)
- One of the most common indications for hospitalization
- Neonates have a high risk of invasive bacterial infection (IBI) or a viral infection; most severe is HSV
- Presentation of illness can be subtle with history of poor feeding, lethargy, and decreased activity

Diagnosis

CBC with differential; complete metabolic panel; cultures of blood, urine, and cerebrospinal fluid (CSF)

Most common bacterial pathogens:

- Early onset (< 30 days): Predominantly GBS infection, followed by gram ⊖ organisms (predominantly *E coli*), and *Listeria*
- Late onset (>30 days): Predominantly GBS infection, followed by gram ⊖ organisms (predominantly *E coli*)

Treatment

Broad-spectrum antibiotic coverage with ampicillin and cefotaxime

FEVER OF UNKNOWN ORIGIN

- Refers to children with a fever ≥38.3°C (>101°F) for at least 8 days without apparent diagnosis after a careful history, physical examination, and laboratory assessment
- Should include an extensive workup of infections, connective tissue disease, fever, CNS dysfunction, and oncologic disease, especially leukemia
- Often a common disorder with an uncommon presentation

PEDIATRIC NEUROLOGIC DISEASE

CEREBRAL PALSY

A group of nonhereditary, nonprogressive disorders of muscle tone; the most common movement disorder in children. Often results from prenatal, perinatal, or neonatal neurologic insult, but in most cases stems from unknown cause. Risk factors of cerebral palsy (CP) include low BW, intrauterine exposure to maternal infection, prematurity, perinatal asphyxia, trauma, brain malformation, and neonatal cerebral hemorrhage. Pregnant patients at risk for preterm birth are given IV magnesium sulfate to decrease incidence of CP. Categories include the following:

- **Pyramidal (spastic):** A result of damage to the motor cortex. This type presents with spastic paresis of any or all limbs and accounts for 75% of cases. Intellectual disabilities are also present in up to 90% of cases.
- **Extrapyramidal (dyskinetic):** A result of damage to extrapyramidal tracts. Subtypes are choreoathetoid and dystonic (uncontrollable jerking, writhing, or posturing). Abnormal movements worsen with stress and disappear during sleep.
- **Ataxic:** A result of damage to the cerebellum. This type of CP often presents with a lack of body coordination and hypotonia.

History/PE

- May be associated with seizure disorders, behavioral disorders, hearing or vision impairment, learning disabilities, speech deficits, GI disorders, or other associated complications of prematurity.
- Delayed achievement of gross motor and fine motor developmental milestones. Affected limbs may show hyperreflexia, pathologic reflexes (eg, Babinski), ↑ tone/contractures, weakness, and/or underdevelopment. Definite hand preference before 1 year of age is a red flag.
- Toe walking and scissor gait common. Hip dislocations and scoliosis may be seen.

KEY FACT

The most common presenting symptom of cerebral palsy is delayed motor development.

Diagnosis

- Diagnosis is often clinical.
- Imaging can be used to determine the underlying cause of CP in some cases. Ultrasonography may be useful in infants to identify intracranial hemorrhage or structural

malformations. MRI can be diagnostic. Electroencephalography (EEG) may be useful in patients with suspected seizures.

- A full evaluation of hearing, vision, and developmental milestones (especially motor) should be done if there is suspicion of CP.

Treatment

- There is no cure for CP. Multidisciplinary treatment is required. Special education, physical therapy, braces, and surgical release of contractures may help.
- Spasticity can be treated with baclofen, diazepam, or dantrolene. Botulinum toxin can be helpful for localized spasticity. Baclofen pumps and posterior rhizotomy (nerve destruction for pain relief) may alleviate severe contractures.

FEBRILE SEIZURES

Usually occur in children between 6 months and 5 years of age who have no evidence of intracranial infection or other causes. Risk factors include a rapid ↑ in temperature and a history of febrile seizures in a close relative. Febrile seizures recur in approximately one in three patients.

History/PE

- Seizures usually occur during the onset of fever and may be the first sign of an underlying illness (eg, otitis media, roseola).
- **Classified as simple or complex:**
  - **Simple:** A short (<15 minutes), generalized tonic-clonic seizure with one seizure in a 24-hour period and return to neurologic baseline shortly afterward. A high fever (>39°C [>102.2°F]) within hours of the seizure is typical.
  - **Complex:** A long (>15 minutes) seizure, focal seizure, or multiple seizures in a 24-hour period or no return to neurologic baseline. A low-grade fever for several days before seizure onset may be present.
- **Febrile status epilepticus:** Prolonged continuous seizures (30 minutes) or intermittent seizures without return to baseline in between.

Diagnosis

- Often a clinical diagnosis, with exclusion of CNS abnormalities, inflammation, or metabolic dysfunction that can account for the seizure.
- Focus on finding source of infection. LP and CSF studies are indicated if there are concerns for clinical signs of CNS infection (eg, altered consciousness, meningismus, a tense/bulging anterior fontanelle) after ruling out ↑ ICP.
- No workup necessary for first-time simple febrile seizures, and no laboratory studies needed if consistent with febrile seizures. Infants <6 months of age need a sepsis workup (CBC; urinalysis [UA]; and blood, urine, and CSF culture).
- For atypical presentations, electrolytes, serum glucose, blood cultures, UA, and CBC with differential and additional studies as applicable to concerns.

KEY FACT

Only perform an LP if CNS infection is suspected in a patient with a febrile seizure. Keep in mind that if a patient is on antibiotics, it can mask symptoms of an infection.

Treatment

- First-time febrile seizures can be managed with observation and parental counseling.
- Seizures >5 minutes should be treated with anticonvulsant medications (eg, benzodiazepines). Febrile status epilepticus can be treated with fosphenytoin.
- Patient can be treated with antipyretics (acetaminophen; avoid ASA in light of the risk for Reye syndrome, acute liver failure, and encephalopathy), and any underlying illness should be addressed. Note that antipyretic therapy does not ↓ the recurrence of febrile seizures.
- For complex seizures, the physician should conduct a thorough neurologic evaluation, including EEG and MRI. Chronic anticonvulsant therapy (eg, diazepam or phenobarbital) is only needed if abnormalities are found; usually not necessary.

Complications

- The risk for recurrence is about 30% to 35% and is highest within 1 year of the initial episode. For simple febrile seizures, there is no ↑ risk for developmental abnormalities and only slight association with this being an early manifestation of an underlying epilepsy.
- Risk factors for the development of epilepsy include complex febrile seizures (~10% risk), ⊕ family history of epilepsy, an abnormal neurologic examination, and developmental delay.

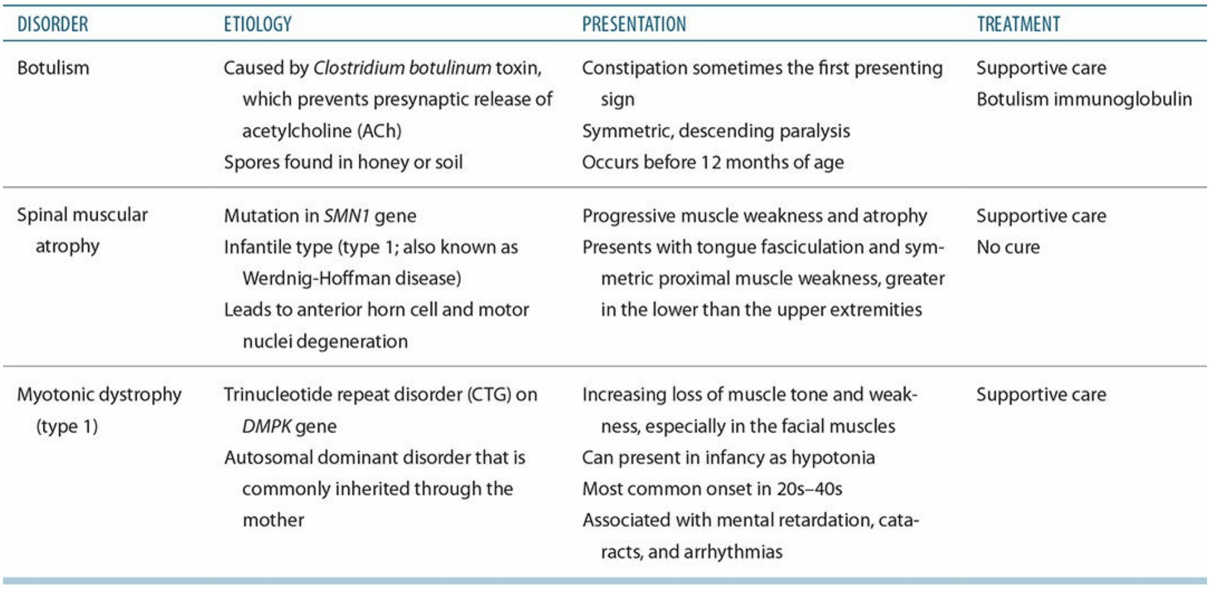
KEY FACT

Simple febrile seizures do not cause brain damage, do not ↑ risk for developmental abnormalities, recur in about 30%–35% of cases, and only slight association with this being an early manifestation of an underlying epilepsy.

INFANTILE HYPOTONIA

The lack of tone or resistance of muscle movement. It differs from weakness, which is the decrease in active muscle contraction. Common causes of infantile hypotonia are listed in Table 2.12-24.

TABLE 2.12-24. Common Causes of Infantile Hypotonia



DISORDER	ETIOLOGY	PRESENTATION	TREATMENT
Botulism	Caused by *Clostridium botulinum* toxin, which prevents presynaptic release of acetylcholine (ACh) Spores found in honey or soil	Constipation sometimes the first presenting sign Symmetric, descending paralysis Occurs before 12 months of age	Supportive care Botulism immunoglobulin
Spinal muscular atrophy	Mutation in *SMN1* gene Infantile type (type 1; also known as Werdnig-Hoffman disease) Leads to anterior horn cell and motor nuclei degeneration	Progressive muscle weakness and atrophy Presents with tongue fasciculation and symmetric proximal muscle weakness, greater in the lower than the upper extremities	Supportive care No cure
Myotonic dystrophy (type 1)	Trinucleotide repeat disorder (CTG) on *DMPK* gene Autosomal dominant disorder that is commonly inherited through the mother	Increasing loss of muscle tone and weakness, especially in the facial muscles Can present in infancy as hypotonia Most common onset in 20s–40s Associated with mental retardation, cataracts, and arrhythmias	Supportive care

COMMON BRAIN NEOPLASMS IN CHILDREN

Table 2.12-25 outlines pediatric cranial neoplasms.

TABLE 2.12-25. Common Primary Neoplasms in Children

TUMOR	PATHOLOGY	PRESENTATION	TREATMENT
Pilocytic astrocytoma (Images A and B)	Generally benign, well-circumscribed tumor of astrocyte origin; stains ⊕ for glial fibrillary acidic protein (GFAP) Posterior fossa/infratentorial tumor	Most common CNS tumor in children Presents with drowsiness, headache, ataxia, nausea, vomiting, cranial neuropathy Slow growing with protracted course and favorable prognosis Bipolar neoplastic cells with hairlike projections; associated with microcysts and Rosenthal fibers (eosinophilic, corkscrew fibers); cystic + solid mass (gross)	Resection if possible; radiation
Medulloblastoma (Image C)	A primitive neuroectodermal tumor (PNET) of the posterior fossa/infratentorial region Arises from the fourth ventricle or cerebellar vermis Homer-Wright rosettes, small blue cells Synaptophysin ⊕	Highly malignant but radiosensitive; may seed the subarachnoid space or spread "drop metastases" to the spinal cord May cause obstructive hydrocephalus by compressing the fourth ventricle → headaches, papilledema, vomiting Truncal ataxia caused by involvement of cerebellar vermis	Surgical resection coupled with radiation and chemotherapy
Ependymoma	Ependymal cell tumor most commonly found in the fourth ventricle, but may present as primary spinal cord tumors Characteristic perivascular pseudorosettes; rod-shaped blepharoplasts (basal ciliary bodies) found near the nucleus	Causes obstructive hydrocephalus by compressing the fourth ventricle → headaches, papilledema, vomiting Myelopathy and radiculopathy possible presenting symptoms with involvement of spinal cord	Surgical resection followed by radiation or chemotherapy
Craniopharyngioma (Images D and E)	The most common suprasellar tumor in children Calcification common (distinguishes it from pituitary adenoma) Derived from remnants of Rathke pouch (ectoderm); cholesterol crystals found in "motor oil"–like fluid within tumor	Benign Most commonly causes bitemporal hemianopsia due to compression of the optic chiasm Associated with a high recurrence rate	Surgical resection
Pinealoma	Germ cell tumor of pineal gland; similar to other germ cell tumors (eg, testicular seminoma) Mass arising in the third ventricle	Malignant Can cause Parinaud syndrome (compression of tectum → vertical gaze palsy); obstructive hydrocephalus (compression of cerebral aqueduct); precocious puberty in males (human chorionic gonadotropin [hCG] production)	Radiation therapy ± chemotherapy

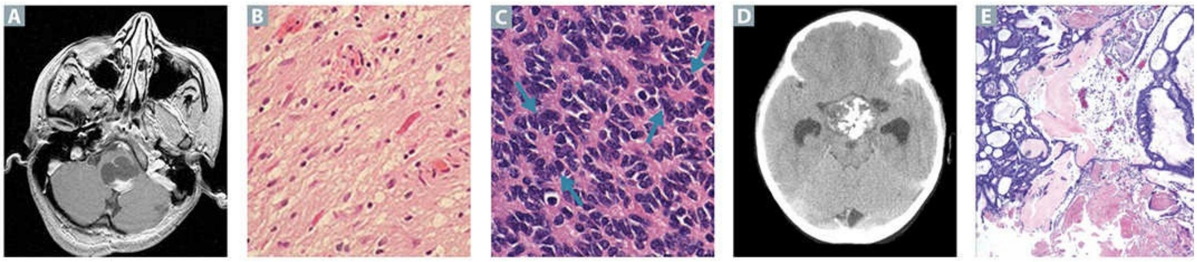


Image A modified with permission from Hafez, R.F. Stereotaxic gamma knife surgery in treatment of critically located pilocytic astrocytoma: preliminary result. *World J Surg Onc 5*, 39 (2007). https://doi.org/10.1186/1477-7819-5-39. Image D reproduced with permission from Garnett, M.R., Puget, S., Grill, J. et al. Craniopharyngioma. *Orphanet J Rare Dis 2*, 18 (2007). https://doi.org/10.1186/1750-1172-2-18. Images B, C, and E reproduced with permission from USMLE-Rx.com.

SPINAL DYSRAPHISM

A type of neural tube defect (NTD) caused by improper closure of the neural tube, leading to a potentially exposed spine or spinal cord. An important risk factor is due to folate deficiency during pregnancy.

History/PE

- Patients have varying clinical presentations, depending on the type of spinal dysraphism.
- Closed spinal dysraphism includes:
  - Spina bifida occulta: Most common type. Caused by a defect in the vertebrae with intact meninges or spinal cord. Patients are usually asymptomatic with a tuft of hair or dimple at the level of the defect.
- Open spinal dysraphism includes:
  - Meningocele: The meninges protrude through the vertebral defect. The spinal cord is often undamaged.
  - Myelomeningocele: This is the most severe variation. A portion of the spinal cord herniates through the vertebral defect.

Diagnosis

Open spinal dysraphism is often detected by an elevated level of α-fetoprotein (AFP) in a quad screen during pregnancy. Ultrasound can then be used to rule out other causes of elevated AFP (eg, multifetal gestation).

Treatment

Closed spinal dysraphism can be treated with monitoring, as patients are often asymptomatic. Open spinal dysraphism is more severe and should be treated with surgery within 3 days of birth to reduce any chances of infection. Long-term management includes multidisciplinary and interdisciplinary teams to optimize neuromuscular function.

BREATH-HOLDING SPELLS

Breath-holding spells are nonepileptic paroxysmal episodes that typically occur between 6 months and 6 years of age. The spells are brief periods when young children stop breathing for up to 1 minute. The spells can cause the child to lose consciousness and often occur when a young child is angry, frustrated, in pain, or afraid, but the spell is a reflex. There is a significant association between breath-holding spells and certain types of anemia, particularly iron-deficiency anemia. A family history of breath-holding spells is also present in a significant portion of patients.

KEY FACT

Breath-holding spells are triggered by an emotional trigger and may result in loss of consciousness or cyanosis. Although they may be alarming to the parents, these are benign episodes and not cardiac related. They typically resolve by 5 years of age.

History/PE

Cyanotic variant: Most common. The episode is generally preceded by an upsetting event such as a reprimand or temper tantrum. A stereotypical sequence ensues with a period of crying followed by forced apnea and loss of tone and consciousness. Cyanosis is very marked.

Pallid variant: More often in response to a very mild trauma to the head or upper body. The child then becomes pale and diaphoretic with loss of tone and consciousness.

Diagnosis

The diagnosis is a clinical one. The episode must be distinguished from a seizure by careful history taking. A workup to identify anemia is recommended with hemoglobin and ferritin. The prognosis is excellent, with a complete resolution of spells in the vast majority of children by 8 years of age.

Treatment

Treatment is limited to correcting an iron-deficiency anemia; correcting this can reduce the frequency of spells in some children. Antiepileptics are not recommended, and seizures generally resolve over time.

RETT SYNDROME

Rett syndrome is a neurodevelopmental disorder. It is due to a mutation in the *MECP2* gene on the X chromosome and is most commonly sporadic. It is almost exclusively seen in females, as males with the condition die almost immediately after birth. Manifestations begin around 6 to 18 months of age in girls.

History/PE

Clinically, signs and symptoms typically begin after a period of normal growth and development. The earliest sign is the deceleration of head growth. Subsequently, patients will progressively lose communication skills, fine motor skills, and intellectual abilities. A distinctive feature of the condition is the development of stereotypical hand movements such as grasping of hair or clothing and episodes of inconsolable irritability.

Additional manifestations include the following:

- Loss of spoken language
- Motor dysfunction
- Scoliosis
- Growth failure (head circumference first and then height and weight)
- Epilepsy
- Decreased bone mineral density
- Cardiac defects/autonomic dysfunction
- Sleep dysfunction
- Abnormal breathing during wakefulness

Diagnosis

The clinical suspicion of Rett syndrome is confirmed by a DNA analysis showing mutations in the *MECP2* gene.

Treatment

Treatment is largely supportive. Currently no disease-modifying treatments are routinely used. Patients are usually managed by a multidisciplinary team with physical, occupational, and communication therapy. Growth, nutrition, cardiac function, sleep, and neurologic function should be monitored.

CHIARI MALFORMATIONS

Congenital malformations are due to underdevelopment of the posterior fossa. There are two main types: Chiari I and Chiari II:

- Chiari I: Herniation of the cerebellar tonsils through the foramen magnum (I structure) (Fig. 2.12-21A). Typically presents after childhood with occipital headaches and cerebellar symptoms (ataxia, dizziness). Headaches are worse with Valsalva maneuver (eg, cough). Chiari I is associated with syringomyelia.

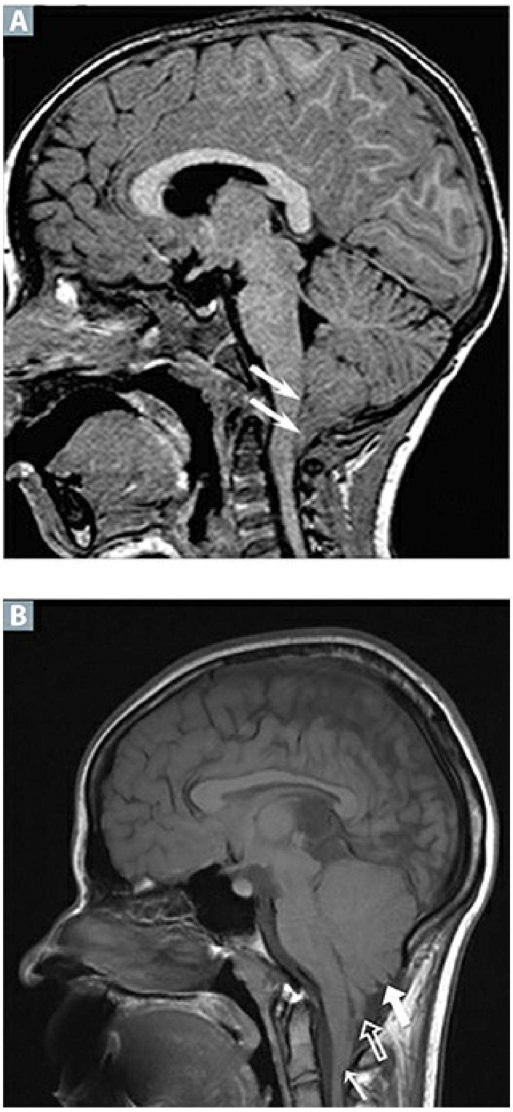


FIGURE 2.12-21. **Chiari malformations. (A)** outlines the herniation of the tonsils only *(white arrows)* in Chiari I. **(B)** outlines the herniation of the medulla *(thin white arrow)*, tonsils *(transparent white arrow)*, and vermis *(thick white arrow)* in Chiari II. (Image A adapted with permission from Toldo I, De Carlo D, Mardari R, et al. Short lasting activity-related headaches with sudden onset in children: a case-based reasoning on classification and diagnosis. *J Headache Pain.* 2013;14[1]:3 doi:10.1186/1129-2377-14-3. Image B reproduced with permission from Geerdink N, van der Vliet T, *Rotteveel* JJ, et al. Essential features of Chiari II

malformation in MR imaging: an interobserver reliability study—part 1. *Childs Nerv Syst.* 2012;28[7]:977-985. doi:10.1007/s00381-012-1761-5.)

- Chiari II: Herniation of cerebellar tonsils, vermis, and medulla through the foramen magnum (Fig. 2.12-21B). Presents at birth with apnea, stridor, dysphagia due to medullary compression, and noncommunicating hydrocephalus due to aqueductal stenosis. Chiari II is associated with lumbosacral myelomeningocele, which can cause lower limb motor weakness/sensory loss.

BENIGN FAMILIAL MICROCEPHALY AND MACROCEPHALY

Microcephaly is defined as head circumference >2 standard deviations below the mean, whereas macrocephaly entails head circumference >2 standard deviations above the mean. Diagnosed in normal, healthy children with a normal parent with a similar-sized head. Development and examination will be normal with no syndromic features.

PEDIATRIC HEMATOLOGY

DIAMOND-BLACKFAN ANEMIA

A congenital form of pure red cell aplasia (causes isolated anemia versus Fanconi anemia, which causes pancytopenia; see Table 2.12-26). It is due to an intrinsic defect in erythroid progenitor cells, leading to macrocytic normochromic anemia. Patients have an increased malignancy risk (acute myelogenous leukemia [AML], myelodysplastic syndrome [MDS)], and solid tumors, eg, colon cancer). Other long-term complications include endocrine dysfunction (short stature, adrenal insufficiency, hypogonadism, hypothyroidism, vitamin D deficiency) and hemosiderosis.

TABLE 2.12-26. Congenital Anemias

	DIAMOND-BLACKFAN ANEMIA	FANCONI ANEMIA
Inheritance pattern	Autosomal dominant	Autosomal recessive or X-linked
Gene mutation effect	Impaired ribosome synthesis	Chromosome fragility
Type of anemia	Macrocytic-normochromic	
Anemia age of onset	Classically presents in infancy	Around 8 years
Congenital anomalies	Present	Present
Malignancy risk	Present	Present
CBC findings	Isolated macrocytic anemia	Pancytopenia
Specific testing	Elevated erythrocyte adenosine deaminase, elevated hemoglobin F	Chromosome breakage assay
Treatment	Corticosteroids, blood transfusions, stem cell transplant	Androgens, blood transfusions, stem cell transplant

History/PE

- Progressive anemia within first year of life → signs and symptoms of impaired oxygen-carrying capacity (eg, pallor, tachycardia, apnea, lethargy). Low BW, growth restriction usually present.
- Associated with congenital abnormalities (up to 50% cases, mainly in head and upper limb). Craniofacial (low-set ears, micrognathia, cleft palate, broad nasal bridge), ophthalmologic (congenital cataracts or glaucoma), cardiac (ASD, VSD), upper extremity malformations (triphalangeal thumbs), intellectual disability, hypogonadism, and short stature.

Diagnosis

- CBC: ↓ hemoglobin (Hb), ↑ mean corpuscular volume (MCV), normal WBC and platelet count; reticulocytopenia: ↑ %HbF (but ↓ total Hb)
- Normal bone marrow cellularity with markedly decreased or absent erythroid precursors
- Specific testing: ↑ erythrocyte adenosine deaminase (eADA) activity
- **Four diagnostic criteria (all must be present):**
  - Onset of anemia at age <1 year
  - Macrocytic anemia without cytopenias
  - Reticulocytopenia
  - Normal marrow cellularity with a paucity of erythroid precursors

Treatment

- Corticosteroids (children ≥1 year old), RBC transfusions (infants <1 year old or steroid-refractory patients), stem cell transplant (steroid-refractory patients)

- Corticosteroids avoided in infants due to ↑ risk of adverse effects
- Monitoring for development of malignancies and iron overload, hemosiderosis (among patients who received chronic transfusion therapy)

FANCONI ANEMIA

Autosomal recessive or X-linked disorder of chromosomal fragility. People of Ashkenazi Jewish descent ↑ carrier frequency. Genetic mutation of multiple DNA cross-link repair genes → impaired cellular repair of DNA cross-links → impaired cell cycle regulation, genomic instability → increased sensitivity to cytotoxic therapies and a predisposition for blood/solid malignancies (eg, AML, MDS, squamous cell cancers) and hematopoietic stem cell loss (→ bone marrow failure → macrocytic-normochromic anemia, pancytopenia). There are many other causes of bone marrow failure, which are described in Table 2.12-27.

TABLE 2.12-27. **Causes of Bone Marrow Failure**

INHERITED BONE MARROW FAILURE SYNDROMES	ACQUIRED BONE MARROW FAILURE
Fanconi anemia	Acquired aplastic anemia (due to drugs, chemicals, radiation)
Shwachman-Diamond syndrome	Acquired aplastic anemia (associated with viral infections such as parvovirus, immune disorders)
Diamond-Blackfan anemia	Myelodysplastic syndromes
Thrombocytopenia absent radius	Paroxysmal nocturnal hemoglobinuria
Severe congenital neutropenia	
Amegakaryocytic thrombocytopenia	

History/PE

- Usually present within first 8 years of life. Pancytopenia: Neutropenia → life-threatening infections; thrombocytopenia → bleeding risk, bruising, anemia → signs and symptoms of impaired oxygen-carrying capacity (eg, pallor, tachycardia, apnea, lethargy).
- Associated with congenital abnormalities: Short stature, microcephaly, developmental delay, café au lait skin lesions, and malformations belonging to the VACTERL-H association. For an explanation of VACTERL-H, see the Mnemonic box.

Diagnosis

- CBC (↓ Hb, ↓ absolute neutrophil count, ↓ platelet count); ↓ absolute reticulocyte count
- Hypocellular bone marrow
- Specific testing: Chromosome breakage assay

Treatment

- Allogeneic hematopoietic cell transplantation (HCT) (curative therapy for Fanconi anemia–associated bone marrow failure, MDS, and leukemia).
- Androgen therapy (eg, oxymetholone), growth factors (eg, granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]), blood transfusion (leukoreduced, irradiated packed cell or platelet) therapy.
- Screening, monitoring for malignancies. First-degree relatives of affected patient should be tested and provided genetic counseling.

CYCLIC NEUTROPENIA

Cyclic neutropenia is a rare genetic disorder characterized by consistent, symptomatic, and recurrent neutropenia (usually every 3 weeks). Associated with mutation of *ELANE* gene (encodes neutrophil elastase). Commonly affects children (equal sex predisposition). Cyclic neutropenia causes death, usually due to NEC, peritonitis, or sepsis. It is not associated with malignant transformation to MDS or AML.

THROMBOCYTOPENIA ABSENT RADIUS SYNDROME

Thrombocytopenia absent radius (TAR) syndrome is an autosomal recessive disorder that is caused by a deletion and/or mutation in the *RBM8A* gene. Characterized by hypomegakaryocytic thrombocytopenia and bilateral radial bone aplasia in the presence of thumbs (usually absent or hypoplastic in Fanconi anemia). TAR can be precipitated by stress, infection, or allergy to cow's milk. Intracranial hemorrhage results in increased mortality.

History/PE

- Presents with frequent nosebleeds or GI bleeding, bruising, life-threatening hemorrhages (due to thrombocytopenia), and radial aplasia. Ninety percent of individuals present with symptomatic thrombocytopenia by age 4 months, but patients improve with age.
- Frequent cow's milk allergy (→ vomiting, bloody diarrhea, and failure to thrive).
- Associated with cardiac defects (ASD, VSD, TOF), facial defects (micrognathia; tall, broad forehead, hypertelorism), and lower extremity defects (hip dislocation, femoral and tibial torsion).

Diagnosis

- **CBC:** Thrombocytopenia is present. ↑ eosinophil count may be found (50% of cases). ↑ WBC or ↓ Hb may also be found.
- **X-ray of the forearm:** Imaging shows characteristic absent radii and presence of thumbs.
- **Bone marrow biopsy:** This is not required for diagnosis but can help exclude other differentials.
- **Molecular testing**: Deletion or duplication analysis of *RBM8A* gene can confirm diagnosis.

Treatment

- Platelet transfusion, hematopoietic stem cell transplantation (persistent bleeding despite platelet transfusion)
- Splinting of the hands
- Avoiding trauma, antiplatelet drugs, or prolonged pressure on injection sites

KASABACH-MERRITT SYNDROME

A life-threatening coagulopathy of infancy classically characterized by thrombocytopenia, microangiopathic hemolytic anemia, and consumptive coagulopathy. Occurs as a complication of a rapidly growing vascular tumor (kaposiform hemangioendothelioma and tufted angioma). Intravascular coagulation with platelet trapping → thrombocytopenia, fibrinogen consumption and degradation, consumption of coagulation factors → disseminated intravascular coagulation (DIC). These benign vascular tumors are aggressive. Complications include reactive hemarthrosis (→ hemophilia-like arthropathy), congestive cardiac failure, and GI bleeding. Kasabach-Merritt syndrome has a high mortality rate due to life-threatening bleeding, cardiac failure, and/or local invasion into structures.

History/PE

- Kasabach-Merritt syndrome presents in infancy with an enlarging, firm, purpuric cutaneous or soft tissue lesion, as shown in Figure 2.12-22. Most commonly in the trunk, extremities, or retroperitoneum. It may be associated with overlying hypertrichosis or hyperhidrosis.

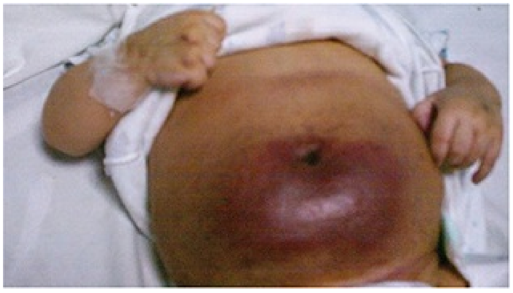


FIGURE 2.12-22. Large abdominal capillary hemangioma in an infant (Reproduced with permission from Abass K, Saad H, Kherala M, et al. Successful treatment of Kasabach-Merritt syndrome with vincristine and surgery: a case report and review of literature. *Cases J.* 2008;1[9]:393. https://doi.org/10.1186/1757-1626-1-9.)

- Cutaneous lesions (10% of cases) present with a rapidly enlarging lesion that turns painful, swollen, and/or purpuric or ecchymotic. Retroperitoneal lesions are often missed on physical examination and thus are diagnosed late.

Diagnosis

- CBC: ↓ Hb, ↓ platelets. Burr cells and schistocytes may be present on peripheral blood film (PBF) in microangiopathic hemolytic anemia.
- Prolonged PT, aPTT, ↓ fibrinogen, ↑ D-dimer, ↑ fibrin degradation products ([FDPs] in severe DIC)
- Ultrasound, CT scan, or MRI of suspected tumor can be performed to assess extent of the visible lesion or to evaluate visceral lesions. Tumor biopsy is contraindicated due to bleeding risk.

Treatment

- Definitive treatment is surgical resection of the tumor.
- If the tumor is not amenable to surgery, various other modalities with varying efficacy are available: systemic corticosteroids, radiation therapy, pneumatic compression, embolization and/or pharmacotherapy (eg, α-interferon, platelet aggregation inhibitors, chemotherapy, particularly vincristine).

SICKLE CELL DISEASE

An autosomal recessive disorder caused by a mutation of adult hemoglobin (the β-chain has Glu replaced by Val, causing production of an abnormal β globin chain), resulting in the production of HbS rather than HbA. HbA_2 and HbF are still produced. It is common in patients of sub-Saharan African descent. The homozygote (SS) has sickle cell anemia (HbSS), and the heterozygote (HbAS) has sickle cell trait, which causes no disability (it does uniquely protect against *Plasmodium falciparum* malaria). Signs and symptoms of sickle cell disease are caused by ↓ RBC survival and a tendency of sickled cells to aggregate and cause vaso-occlusion.

KEY FACT

Sickling occurs with dehydration and deoxygenation and at high altitude. As it happens in the vasa recta (vessels supplying the inner medulla of the kidneys), sickle cell patients have ↓ ability to concentrate urine, presenting as polyuria or nocturia.

History/PE

- Classic presentation of pain crisis: Patient of sub-Saharan African descent with sudden onset of severe chest pain, back pain, or thigh pain. Pain may be accompanied by fever.
- Acute chest syndrome: Pulmonary infiltrations involving complete lung segments and causing chest pain, fever, wheezing, coughing, and tachypnea. Chief causes of infiltration are fat embolism from bone marrow or infection with *S pneumoniae*, *Mycoplasma*, *Chlamydia*, or viruses.
- May first present with dactylitis in childhood (bilateral hand/foot swelling).
- Lifelong hemolysis results in anemia, jaundice, pigmented cholelithiasis, ↑ cardiac output ([CO] murmur, eventual CHF), and delayed growth.
- Chronic hemolysis is usually well tolerated, except in an acute, painful vaso-occlusive crisis ([VOC], commonly caused by microvascular occlusion), which stems from infection/fever, hypoxia, dehydration, and cold temperatures.
- Other VOC: Dactylitis (occurs <3 years of age), mesenteric ischemia (mimics acute abdomen), CNS infarction (leads to stroke, cognitive defects, or seizures), priapism, and avascular necrosis (AVN) of the femoral head. Leads to ischemic organ damage, especially splenic infarction (typically occurs <2 years of age), which predisposes to infection from encapsulated organisms, particularly pneumococcal sepsis and acute chest syndrome (pneumonia and/or pulmonary infarction; see Fig. 2.12-23). Patient is also susceptible to osteomyelitis and to chronic kidney disease (sickle cell nephropathy).

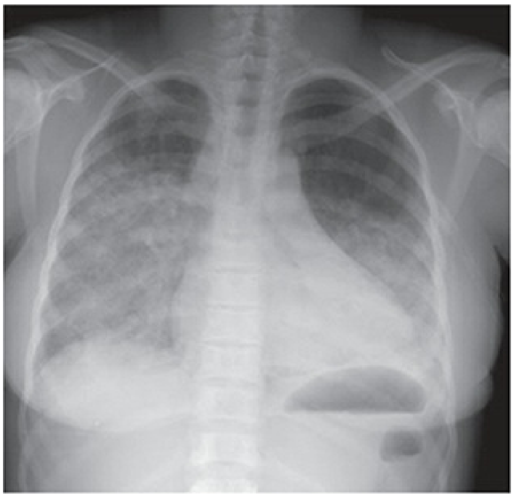


FIGURE 2.12-23. Acute chest syndrome. Frontal CXR of a 19-year-old woman with sickle cell disease and acute chest pain. Note the bilateral lower and midlung opacities and mild cardiomegaly. (Reproduced with permission from USMLE-Rx.com.)

- Other complications**:** Splenic sequestration (sudden pooling of blood into the spleen resulting in hypovolemia) and aplastic crisis (secondary to infection with viruses such as parvovirus B19). Both complications present with ↓ hematocrit but are distinguished clinically by ↓ reticulocytes in aplastic crisis (secondary to bone marrow involvement) and ↑ reticulocytes in splenic sequestration.

- Sickle cell trait (HbAS) is relatively benign. Patients have normal Hb and RBC morphology. However, renal complications include hematuria (renal papillary necrosis), defect in the ability to concentrate urine (hyposthenuria), and ↑ risk for UTIs.

KEY FACT

The most common cause of osteomyelitis in patients with sickle cell disease is *Staphylococcus aureus; Salmonella* is the second most common cause. Patients are also at ↑ risk for avascular necrosis of the femoral head.

Diagnosis

- **Best initial test:** CBC (↑ reticulocytes, ↑ indirect bilirubin) with peripheral smear showing sickle cells and Howell-Jolly bodies (see Fig. 2.12-24)

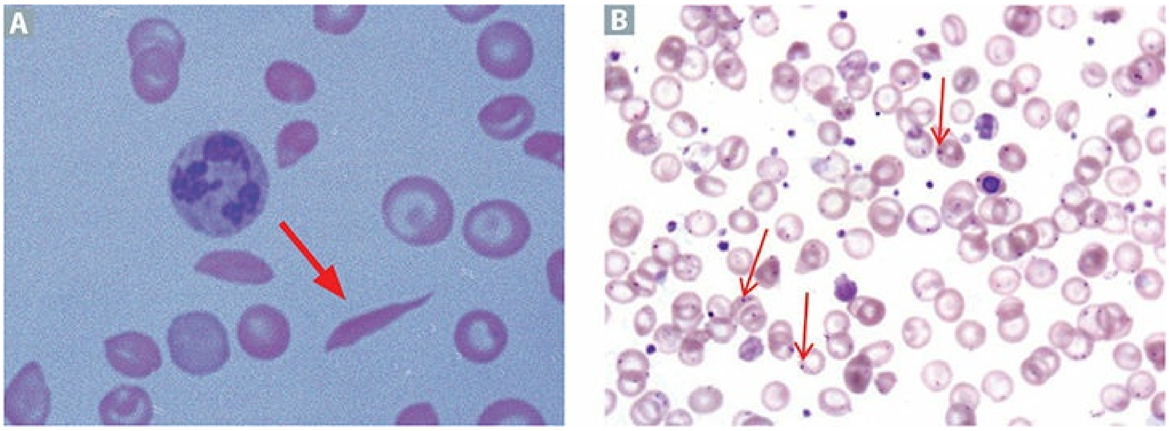


FIGURE 2.12-24. **Sickle cell disease. (A)** Sickle-shaped RBCs *(arrow)* are almost always seen on blood smear, regardless of whether the patient is having a sickle cell crisis. **(B)** Howell-Jolly bodies, which suggest functional hyposplenia or asplenia. (Image A reproduced with permission from Dr. Peter McPhedran, Yale Department of Hematology. Image B reproduced with permission from Serio B, Pezzullo L, Giudice V, et al. OPSI threat in hematological patients. *Transl Med UniSa*. 2013;6:2-10.)

- Most accurate test: Hemoglobin electrophoresis

MNEMONIC

Causes/triggers of acute VOC in sickle cell disease—

HIDe in the COLD

Hypoxia
Infections/fever
Dehydration
COLD temperatures

Treatment

- Management of chronic disease:
  - Treat with hydroxyurea, which stimulates the production of fetal hemoglobin and helps prevent the recurrence of sickle cell crises. Hydroxyurea is teratogenic and may cause mild myelosuppression (important to monitor WBCs).
  - If hydroxyurea does not prove effective, chronic transfusion therapy, which carries the risk for iron overload, can be attempted.
  - Folic acid supplementation is often required to prevent macrocytic anemia caused by frequent RBC turnover.
  - The risk exists for septicemia in febrile patients or in leukocytosis. Have low threshold to give antibiotics (use ceftriaxone, levofloxacin, or moxifloxacin).
  - Patients with autosplenectomy benefit from prophylactic pneumococcal vaccination and antibiotics (penicillin in patients <5 years of age) since they are at ↑ risk for infection from encapsulated bacteria. Treat recurrent cholelithiasis with cholecystectomy.
- Management of **sickle cell crises:**
  - Patients with VOC require pain to be treated with adequate analgesia (pain management), O_2 therapy, IV fluid rehydration, and antibiotics (if infection is suspected to be the trigger).
  - If there is concern of a VOC progressing to acute chest syndrome, initiate aggressive hydration, antibiotics, and incentive spirometry. Keep the sickle variant <40%. This can be done with simple transfusions or, if necessary, exchange transfusion in an intensive care unit (ICU) setting. Bronchodilators may be helpful.
- No treatment is required for sickle cell trait (HbAS).

PEDIATRIC ONCOLOGY

LEUKEMIA

A hematopoietic malignancy of lymphocytic or myeloblastic origin. The most common childhood malignancy; 97% of cases are acute leukemias (acute lymphocytic leukemia [ALL] > AML). ALL is most common in non-Hispanic White males between 2 and 5 years of age, whereas AML is seen most frequently in Black boys throughout childhood. Associated with trisomy 21, Fanconi anemia, prior radiation, severe combined immunodeficiency (SCID), and congenital bone marrow failure states, ALL in children has a good prognosis, with a 5-year survival rate >85%.

KEY FACT

ALL is the most common childhood malignancy, followed by CNS tumors and lymphomas.

History/PE

- Symptoms are abrupt in onset. They are initially nonspecific (anorexia, fatigue) and are accompanied by bone pain with a limp or refusal to bear weight and fever (from neutropenia).
- CNS metastases may be associated with headache, vomiting, and papilledema.
- AML can present with a chloroma, a greenish soft tissue tumor of leukemic cells on the

skin or spinal cord.

Diagnosis

- Physical examination: Ecchymoses, petechiae (thrombocytopenia), pallor (anemia), and/or hepatosplenomegaly and lymphadenopathy may be present.
- Laboratory studies: CBC (pancytopenia), coagulation studies, and peripheral blood smear are included. The blood work frequently shows high numbers of blasts (lymphoblasts [ALL] or myeloblasts [AML] are found in 90% of cases). WBC counts can be low, normal, or high.
- A bone marrow aspirate and biopsy for immunophenotyping (terminal deoxynucleotidyl transferase [TdT] assay and a panel of monoclonal antibodies to T- and B-cell antigens) and genetic analysis are necessary to confirm the diagnosis and assess the risk status to inform treatment. The diagnosis is made if bone marrow is hypercellular with ↑ lymphoblasts.
- A CXR can rule out a mediastinal mass (usually thymus).

Treatment

- Chemotherapy based, including induction, consolidation, and maintenance phases. Intrathecal chemotherapy for neurologic prophylaxis is generally added to the treatment regimen.
- Tumor lysis syndrome is common during the initiation of treatment of cancers with high cell turnover (such as leukemias and lymphomas).
  - Caused by the lysis of many neoplastic cells in a short period, resulting in the release of cell contents into the bloodstream.
  - Characterized by hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia (as calcium is bound by phosphate released from the neoplastic cells). It can result in renal failure, arrhythmias, and death.
  - Treatment with fluids, diuretics, and rasburicase (which reduces the risk for urate-induced nephropathy). Allopurinol can be used as a preventive therapy, but rasburicase has been shown to be more effective in treatment. Corticosteroids may precipitate tumor lysis syndrome.

KEY FACT

Watch for tumor lysis syndrome at the onset of any chemotherapy regimen.

MNEMONIC

Electrolytes affected by tumor lysis syndrome—

PUKE Calcium

Phosphorus
Uric acid
K (potassium)
Elevated
Calcium (decreased)

NEUROBLASTOMA

An embryonal tumor of neural crest origin, similar to pheochromocytoma. More than one half of patients are <2 years of age, and 70% have distant metastases at presentation. Neuroblastomas are associated with neurofibromatosis, Hirschsprung disease, Beckwith-Wiedemann syndrome, and the *N-myc* oncogene.

History/PE

- Tumors can be located anywhere along the sympathetic chain, but are most commonly abdominal (in the adrenal medulla, followed by the paraspinal region), thoracic, and cervical (in descending order).
- Symptoms may vary with location and may include abdominal distention with a firm and irregular abdominal mass (may cross the midline), Horner syndrome, hypertension, opsoclonus myoclonus ataxia (“dancing eyes–dancing feet syndrome”), or cord compression (from a paraspinal tumor).
- Patients may have anemia, FTT, and fever.
- More than 50% of patients will have metastases at diagnosis. Signs include bone marrow suppression, proptosis, hepatomegaly, subcutaneous nodules, and opsoclonus/myoclonus.

Diagnosis

- Biopsy of tumor. Histologically appears as small, round, blue tumor cells with a characteristic rosette pattern (see Fig. 2.12-25). Bombesin +.

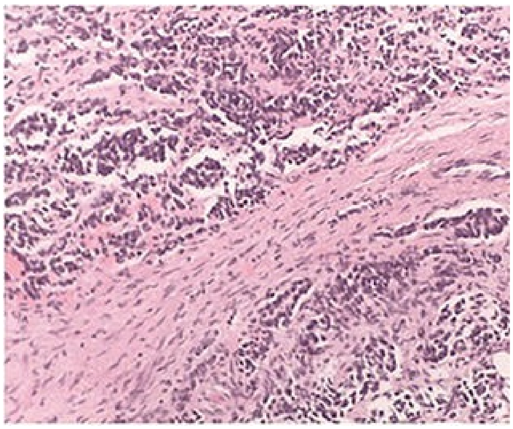


FIGURE 2.12-25. **Neuroblastoma.** (Reproduced with permission from Suffia C, Sorrentino S, Vetrella S, et al. Neuroblastoma presenting with symptoms of epidural compression at birth: a case report. *Ital J Pediatr*. 2016 May 21;42(1):52. doi: 10.1186/s13052-016-0263-6.)

- Elevated 24-hour urinary catecholamines (vanillylmandelic acid and homovanillic acid), CT scan or MRI of suspected tumor.
- Metaiodobenzylguanidine (MIBG) scan and bone marrow aspirate for staging.

Treatment

Local excision plus postsurgical chemotherapy and/or radiation

WILMS TUMOR

A renal tumor of embryonal origin (metanephros) that is most commonly seen in children 2 to 5 years of age. Associated with Beckwith-Wiedemann syndrome (hemihypertrophy, macroglossia, visceromegaly), and WAGR syndrome. Risk factors also include ⊕ family history and horseshoe kidney.

MNEMONIC

WAGR Syndrome

Wilms tumor
Aniridia
Genitourinary abnormalities
Mental **R**etardation [now called “intellectual disabilities”]

History/PE

- Presents as an asymptomatic, nontender, smooth abdominal mass that does not usually cross the midline
- Abdominal pain, fever, hypertension, and microscopic or gross hematuria possible symptoms

Diagnosis

- **Most accurate test:** Biopsy of tumor for definitive diagnosis
- **Best initial test:** Abdominal ultrasonography
- CT scans of the chest and abdomen are used to detect metastases

Treatment

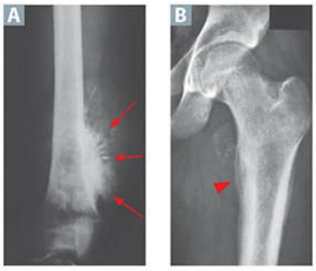
Local resection and nephrectomy with postsurgical chemotherapy and radiation, depending on stage and histology.

CHILDHOOD BONE TUMORS

Bone tumors can be either primary or secondary. Primary bone tumors are most common in the pediatric population. They can also be either benign or malignant—the malignant tumors are important to recognize and treat promptly.

It is critical to distinguish between Ewing sarcoma and osteosarcoma (see Table 2.12-28).

TABLE 2.12-28. Ewing Sarcoma vs Osteosarcoma

VARIABLE	OSTEOSARCOMA	EWING SARCOMA
Origin	Osteoblasts (mesenchyme)	Sarcoma (neuroectoderm); association with chromosome 11:22 translocation
Epidemiology	Commonly seen in Hispanic and White male adolescents; peak incidence is between 13 and 16 years of age	Commonly seen in White males between 10 and 20 years of age
History/PE	Local pain and swelling Systemic symptoms are rare	Local pain and swelling Systemic symptoms (fever, anorexia, fatigue) common
Location	Metaphyses of long bones (distal femur, proximal tibia, proximal humerus) Metastases to lungs in 20%	Diaphysis of long bones (femur, pelvis, fibula, humerus)
Diagnosis  	↑ alkaline phosphatase, ↑ "sunburst" lytic bone lesions (see Image A); Codman triangle possibly found as well MRI of the entire length of the affected bone CT of the chest to rule out pulmonary metastases Radionuclide technetium bone scanning to assess the rest of the skeleton for lesions	Leukocytosis, ↑ ESR Lytic bone lesion with "onion skin" periosteal reaction on x-ray (see Image B) CT of the chest to rule out pulmonary metastases Radionuclide technetium bone scanning to assess the rest of the skeleton for lesions
Treatment	Local excision, chemotherapy	Local excision, chemotherapy, and radiation

Images reproduced with permission from Kantarjian HM et al. *MD Anderson Manual of Medical Oncology*. New York, NY: McGraw-Hill; 2006.

LANGERHANS HISTIOCYTOSIS

Langerhans histiocytosis is a rare pediatric malignancy that results from abnormal proliferation of histiocytes (activated dendritic cells and macrophages). The disease can present with a single or multiple lesions. A common presentation is a solitary, painful lytic bone lesion surrounded by edema. "Tennis racket" granules may be seen on pathology. Single bone lesions are typically treated with surgery alone.

Q

A 14-month-old girl is brought to the pediatrician by her mother for increasing irritability and a 4-pound weight loss in the last month. PE is notable for an ill-appearing child with a well-defined, nodular mass in the left flank that crosses the midline. What is the most likely diagnosis?

PEDIATRIC MUSCULOSKELETAL DISORDERS

COMMON PEDIATRIC ORTHOPEDIC INJURIES

Table 2.12-29 outlines the presentation and treatment of common pediatric orthopedic injuries.

TABLE 2.12-29. Orthopedic Injuries in Children

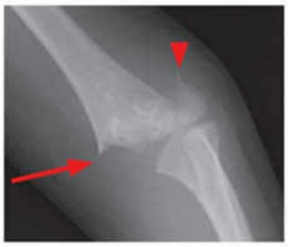
INJURY	MECHANICS	TREATMENT
Clavicular fracture	The most commonly fractured long bone in children; may be birth related (especially in large infants); can be associated with brachial plexus palsies or subclavian artery injury (if concerned, angiography may be done to confirm) Usually involves the middle third of the clavicle, with the proximal fracture end displaced superiorly as a result of the pull of the sternocleidomastoid	Middle third: Rest and ice, sling Distal third: Open reduction and internal fixation
Greenstick fracture	Incomplete fracture involving the cortex of only one side (tension/trauma side) of the bone	Reduction with casting X-rays at 10–14 days
Torus fracture	Buckling of the compression side of the cortex secondary to trauma Usually occurs in the distal radius or ulna from a fall	Cast immobilization for 3–5 weeks
Nursemaid's elbow	Radial head subluxation secondary to being pulled or lifted by the hand Pain, pronation, and refusal to bend the elbow; no sensory deficits or wrist drop	Manual reduction by gentle forearm hyperpronation; alternatively, supination of the forearm at 90 degrees of flexion No immobilization
Supracondylar humerus fracture 	The most common pediatric elbow fracture Tends to occur at 5–8 years of age after a fall on an outstretched hand Injury to median nerve or brachial artery Compartment syndrome possible as pain increases despite analgesics Proximity to the brachial artery increases the risk of Volkmann contracture; the physician should beware of brachial artery entrapment (check radial pulse)	Cast immobilization; closed reduction with percutaneous pinning if significantly displaced
Osgood-Schlatter disease	Overuse apophysitis of the tibial tubercle; causes localized pain, especially with quadriceps contraction, in adolescent athletes	Decreased activity for 2–3 months or until asymptomatic Brace for symptomatic relief
Salter-Harris fracture	Fractures of the growth plate in children. Classified by fracture pattern (**SALTER**): I: Physis (growth plate) (**S**traight across) II: Metaphysis and physis (**A**bove) III: Epiphysis and physis (**L**ower) IV: Epiphysis, metaphysis, and physis (**T**hrough) V: Crush injury of the physis (c**R**ush)	Closed vs. open reduction to obtain appropriate alignment, followed by immobilization

Image reproduced with permission from USMLE-Rx.com.

DUCHENNE MUSCULAR DYSTROPHY

An X-linked recessive disorder resulting from a deficiency of dystrophin, a cytoskeletal protein. Onset is usually at 3 to 5 years of age. Female carriers can be symptomatic, depending on severity of disease.

A

This patient most likely has a neuroblastoma arising from the left adrenal gland. It is the most common solid tumor of childhood and is derived from neural crest cells. Unlike Wilms tumor (nephroblastoma), neuroblastoma is accompanied by systemic symptoms and often crosses the midline. The majority of children have metastases at the time of diagnosis.

History/PE

- Affects axial and proximal muscles more than distal muscles
- May present with progressive clumsiness, fatigability, difficulty standing or walking, increased toe walking, Gowers maneuver (using the hands to push off the thighs when rising from the floor), and waddling gait
- Pseudohypertrophy (fibrofatty replacement of muscle) of the gastrocnemius muscles also seen
- Intellectual disabilities commonly present

Table 2.12-30 outlines the differences between Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD).

TABLE 2.12-30. Duchenne Muscular Dystrophy vs Becker Muscular Dystrophy

CHARACTERISTIC	DUCHENNE MUSCULAR DYSTROPHY	BECKER MUSCULAR DYSTROPHY
Age of onset	3–5 years	5–15 years and beyond
Life expectancy	Teens	30s–40s
Intellectual disabilities	Common	Uncommon
Western blot	Dystrophin is markedly decreased or absent	Dystrophin levels are normal, but protein is abnormal
Serum creatine kinase (CK)	↑ 10–20× normal	↑ 5× normal

Diagnosis

- Creatine kinase (CK) levels >10 to 20 times normal suggest DMD.
- Confirmation is made with genetic testing.
- If genetic testing is inconclusive, muscle biopsy shows replacement of muscle by fat and fibrotic tissue.
- Immunostaining is ⊖ and CK is ↑.
- Electromyography (EMG) shows polyphasic potentials and ↑ recruitment.
- Screening with ECG and echocardiogram can detect dilated cardiomyopathy or conduction abnormalities.

Treatment

Glucocorticoids and physical therapy are necessary to maintain ambulation and to prevent contractures. Liberal use of tendon release surgery may prolong ambulation.

Complications

Death occurs by 20 to 30 years of age due to dilated cardiomyopathy leading to heart failure or respiratory failure.

KEY FACT

A child with a neck mass and head tilt to one side likely has congenital torticollis, caused by fibrosis or spasm of the sternocleidomastoid muscle. First-line treatment involves physical therapy and improved positioning. Plagiocephaly may result if left untreated or if child does not have adequate "tummy time."

MYOTONIC DYSTROPHY

Autosomal dominant disorder causing impaired muscle relaxation (look for "abnormally long handshake" on USMLE). Onset later in life compared to DMD and BMD. Symptoms include difficulty relaxing muscles (myotonia), dysphagia, balding, testicular atrophy, cataracts, and cardiac conduction abnormalities. Type 1 is caused by trinucleotide repeat disorder (**CTG**) on the *DMPK* gene (**C**ataracts, **T**oupee, **G**onads).

SPONDYLOLISTHESIS

Forward slipping of vertebrae (L5 over S1) due to hyperextension of the spine, common in children and adolescents (eg, gymnasts, weightlifters). Presents with bowel and bladder symptoms, lower back pain, and a palpable "step-off" on PE. Associated with congenital malformation of the lumbosacral joints and spondylolysis (pars interarticularis defects).

METATARSUS ADDUCTUS

Congenital deformity of the lower extremity, where the forefoot is turned inward. If the foot is flexible, no surgical treatment is indicated, and the condition is treated with physical therapy and support for spontaneous resolution.

CLUBFOOT (TALIPES EQUINOVARUS)

Congenital deformity of the lower extremity, presenting with forefoot adduction and varus of the calcaneum, talus, and midfoot. In contrast to metatarsus adductus, the foot is not flexible and requires immediate treatment with serial casting. Surgical correction within 3 to 6 months if it does not resolve.

DEVELOPMENTAL DYSPLASIA OF THE HIP

Also called congenital hip dislocation. Excessive hip flexion in utero (eg, breech presentation) leads to excessive stretching of the posterior hip capsule, causing lax musculature and contractures. Developmental dysplasia of the hip can result in subluxation or dislocation of femoral heads and acetabular dysplasia, leading to early degenerative joint disease.

History/PE

- Most commonly found in firstborn girls born in the breech position. ↑ risk occurs with family history.
- **Barlow maneuver:** Posterior pressure is placed on the flexed hip, and then the hip is adducted, leading to an audible "clunk" as the femoral head dislocates posteriorly.

- **Ortolani maneuver:** Thighs are gently abducted from the midline with anterior pressure on the greater trochanter. A soft click signifies a reduction of the femoral head into the acetabulum.
- **Allis (Galeazzi) sign:** The knees are at unequal heights when the hips and knees are flexed in the supine position (the dislocated side is lower).
- Asymmetric inguinal skinfolds that extend beyond the anus and limited abduction of the affected hip are also seen.
- If not treated in infancy, older children present with hip pain and leg length discrepancy, causing a waddling or Trendelenburg gait.
- Figure 2.12-26 outlines the clinical tests and asymmetric skinfolds.

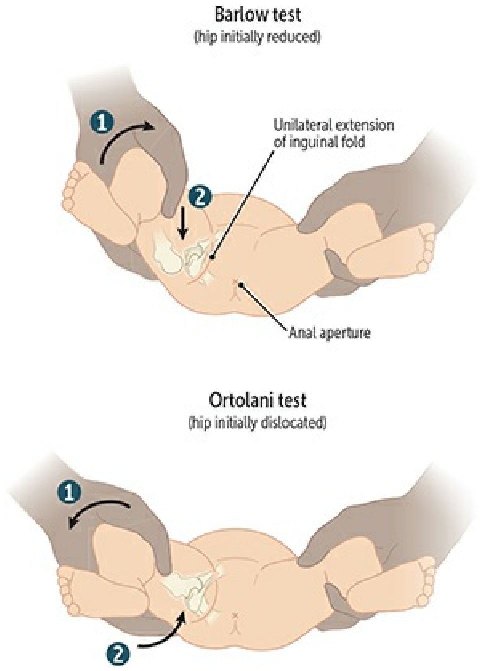


FIGURE 2.12-26. **Developmental dysplasia of the hip.** (Reproduced with permission from USMLE-Rx.com.)

Diagnosis

- Early detection with PE is critical to allow for proper hip development.
- Performing ultrasonography before 4 months of age is recommended, given lack of ossification of the femoral head.
- X-rays are appropriate at >4 months of age.

Treatment

Treatment should begin early even though the condition may resolve on its own before 2 weeks of age.

- **<6 months:** Rigid brace, splint with a Pavlik harness (maintains the hip as flexed and abducted); to prevent AVN, the hips should not be flexed >60 degrees
- **6 to 18 months:** Spica cast
- **>18 months:** Open reduction followed by spica cast

Complications

- Joint contractures and AVN of the femoral head
- Without treatment, significant disability

LEGG-CALVÉ-PERTHES DISEASE

Idiopathic AVN and osteonecrosis of the femoral head (see Fig. 2.12-27). Most common in boys 4 to 10 years of age. Can be a self-limited disease in younger patients, with symptoms lasting <18 months.

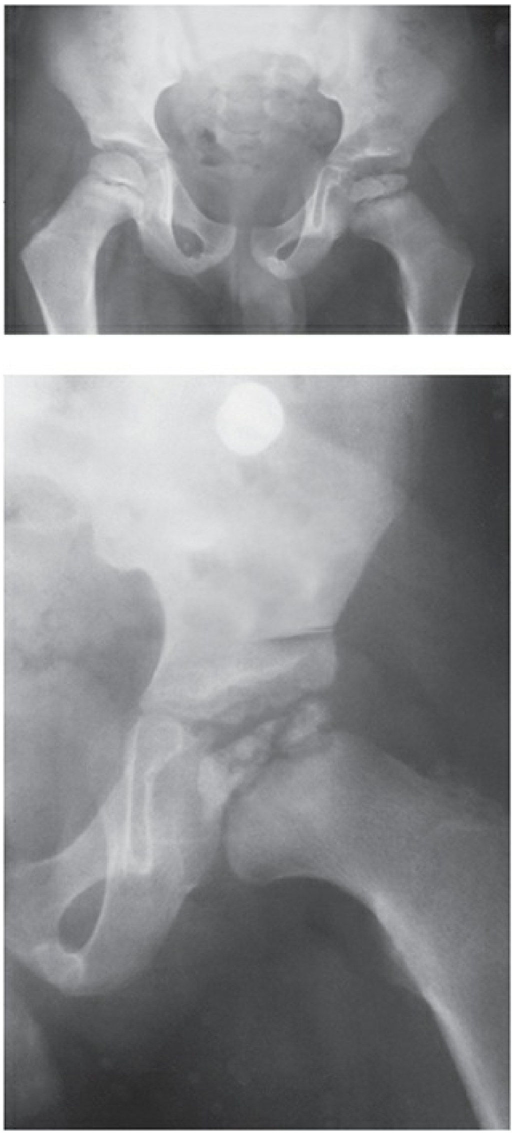


FIGURE 2.12-27. **Legg-Calvé-Perthes disease.** Avascular necrosis of the femoral head showing fragmentation with loss of spherical contour. (Reproduced with permission from Skinner HB. *Current Diagnosis & Treatment in Orthopedics,* 2nd ed. Stamford, CT: Appleton & Lange; 2000.)

History/PE

- Generally asymptomatic at first. Patients can develop a painless limp, antalgic gait, and thigh muscle atrophy.
- Pain sometimes present. If it is present, it can be in the groin or anterior thigh, or it may be referred to the knee.
- Limited abduction and internal rotation; atrophy of the affected leg.
- Usually unilateral (85%–90%).

Diagnosis

Initial x-rays can be normal but later can show a flattened and fragmented femoral head.

Treatment

- Observation is sufficient if limited femoral head involvement or if full range of motion (ROM) is present.
- If extensive necrosis or ↓ ROM, the physician can consider bracing, hip abduction with a Petrie cast, or an osteotomy.
- The prognosis is favorable if the patient is <6 years of age and has full ROM, ↓ femoral head involvement, and a stable joint.

KEY FACT

Legg-Calvé-Perthes disease typically presents as painLESS, whereas slipped capital femoral epiphysis (SCFE) can be painFULL.

SLIPPED CAPITAL FEMORAL EPIPHYSIS

Poor endochondral ossification of the growth plate during a growth spurt and increased shear force cause displacement of the femoral epiphysis from the femoral neck, through the growth plate. The name slipped capital femoral epiphysis (SCFE) is misleading because the epiphysis remains within the acetabulum while the metaphysis moves anteriorly and superiorly. Presents in obese children 10 to 16 years of age; most common hip disorder in adolescence. Associated with trauma, hypothyroidism, and other endocrinopathies.

History/PE

- Insidious onset of dull hip pain, or referred knee pain, and a painful limp
- Restricted ROM and inability to bear weight (differentiates unstable from stable SCFE)
- Bilateral in 40% to 50% of cases
- Limited internal rotation and abduction of the hip; patients hold hip in passive external rotation

MNEMONIC

Differential diagnosis of pediatric limp—

STARTSS HOT

Septic joint
Tumor
Avascular necrosis (Legg-Calvé-Perthes)
Rheumatoid arthritis/JIA
Trauma
Sickle cell disease
SCFE
Henoch-Schönlein purpura
Osteomyelitis
Toxic synovitis

Diagnosis

- X-rays of both hips in anteroposterior and frog-leg lateral views reveal posterior and inferior displacement of the femoral head (see Fig. 2.12-28).

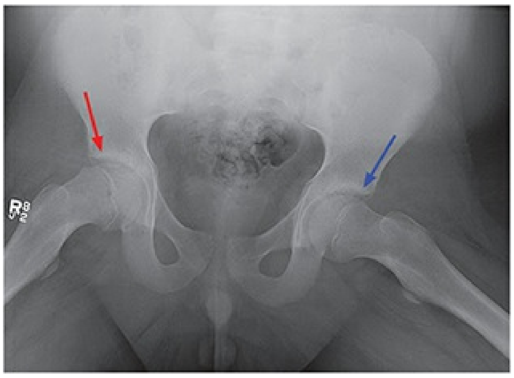


FIGURE 2.12-28. **Slipped capital femoral epiphysis.** Frog-leg anteroposterior x-ray demonstrates medial and inferior displacement of the right femoral epiphysis *(red arrow)* relative to the femoral neck. In comparison, the left side *(blue arrow)* is normal. (Reproduced with permission from USMLE-Rx.com.)

- In patients under the 10th percentile of height, the physician can rule out hypothyroidism with thyroid-stimulating hormone (TSH).

Treatment

- The disease is progressive, so treatment should begin promptly.
- Immediate surgical screw fixation can reduce the risk for AVN.
- No weight-bearing should be allowed until the defect is surgically stabilized.

Complications

Chondrolysis, AVN of the femoral head, and premature hip osteoarthritis requiring arthroplasty.

SCOLIOSIS

A lateral curvature of the spine >10 degrees (Cobb angle). It is sometimes associated with kyphosis or lordosis. Most commonly idiopathic. Develops in early adolescence. Other etiologies are congenital or associated with neuromuscular, vertebral, or spinal cord disease. The male-to-female ratio is 1:7 for curves that progress and require treatment.

History/PE

- Idiopathic disease is usually identified during school physical screening.
- Vertebral and rib rotation deformities are accentuated by the Adams forward bending test.

Diagnosis

X-rays of the spine (posterior, anterior, and full-length views).

Treatment

- Monitoring every 6 months for 10 to 30 degrees of curvature.
- Spinal bracing for ≥30 degrees of curvature in patients with remaining growth. Curvature

may progress even with bracing.

- Surgical correction for ≥40 to 50 degrees of curvature.

Complications

Severe scoliosis can create restrictive lung disease.

CHILD ABUSE

Also known as nonaccidental trauma (NAT); includes neglect and physical, sexual, and psychological maltreatment of children. The physician should suspect abuse if the history is discordant with physical findings or if there is a delay in obtaining appropriate medical care. Certain injuries in children, such as retinal hemorrhages and specific fracture types, are highly suspicious for abuse.

KEY FACT

Suspect sexual abuse if there is genital trauma, bleeding, discharge, or if children have an excessive preoccupation with or knowledge of adult sexual behavior. Vaginal foreign body may be an alternative diagnosis.

History/PE

- Abuse should be suspected if the history is not consistent with the injury pattern or with the child's developmental age—for example, if parents claim their 2-month-old child "rolled off the couch" (developmentally, 2-month-olds cannot roll yet). Abuse also should be suspected if the history continually changes or is vague.
- Look for skin bruising patterns (indicative of the object used), bruises of different ages and color, and burns that are well circumscribed.
- Injuries with high specificity for child abuse include posterior rib fractures, metaphyseal corner "bucket handle" fractures, and spiral fractures of long bones such as the femur (but only before the child can walk, as a spiral fracture may be developmentally appropriate in a walking child).
- **Risk factors:** These include parents with a history of abuse as a child, partner violence, and/or a history of alcohol or drug use; premature children; children with complex medical problems; infants with colic (excessive crying for >3 hours per day for >3 days per week); and repeated hospitalizations
- **Infants:** Abuse or neglect in infants may present as apnea, seizures, feeding intolerance, excessive irritability, somnolence, or FTT.
- **Older children:** Neglect in older children may present as poor hygiene or behavioral abnormalities.
- See Table 2.12-31 for exam findings.

TABLE 2.12-31. **Common Presentations and Mimics of Child Abuse**

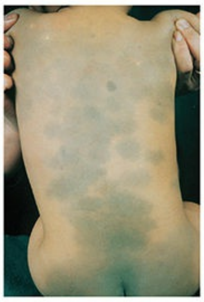
TYPE OF ABUSE	PRESENTATION/IMAGING FINDINGS	MIMICS
Bruises 	Most common physical finding Often located on head and torso May be in pattern reflecting implement (hand, belt)	Congenital dermal melanocytosis, formerly called "Mongolian spots" Coining/cupping (a therapy used in certain cultures where suction cups are attached to the skin) Bleeding diathesis
Burns	Contact burns: Cigarette/curling iron Immersion burns: Hot water; on buttocks, with sparing of flexor surfaces, or stocking-glove distribution with sharp lines of demarcation and uniform burn depth	Scalded skin syndrome, severe contact dermatitis, accidental burn injury
Fractures	Spiral fractures: Humerus/femur (in children not yet walking); epiphyseal-metaphyseal "bucket" fractures Posterior rib fractures: Indication of squeezing	Osteogenesis imperfecta (blue sclerae, hearing loss, opalescent teeth)
Abusive head trauma	Lethargy, feeding difficulty, apnea, seizures, retinal hemorrhage, subdural/epidural hematoma	Accidental head trauma

Image reproduced with permission from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th ed. New York, NY: McGraw-Hill; 2008.

KEY FACT

Osteogenesis imperfecta (OI) is a great mimicker of child abuse and is often tested. It is a genetic disease that affects type I collagen. Those with OI can present with a broad spectrum of clinical features—most classically blue sclera, easy bruising, opalescent teeth, conductive hearing loss, skeletal anomalies, and easily fractured bones.

KEY FACT

In infants, *Neisseria gonorrhoeae* isolated on a vaginal culture is definitive evidence of sexual abuse. *Chlamydia* is not, because it can be acquired from the mother during delivery and can persist for up to 3 years.

Diagnosis

- An x-ray skeletal survey can show fractures in various stages of healing. X-rays may not show fractures until 1 to 2 weeks after injury (although they may show evidence of prior trauma in children <3 years of age). Radionucleotide bone scans (bone scintigraphy) are sometimes used, as they are more sensitive and may show fractures before they are detectable on x-rays; however, they are less specific than plain films.
- If sexual abuse is suspected, the physician should request tests for gonorrhea, syphilis, chlamydia, HIV, and sperm (within 72 hours of assault).
- Abusive head trauma (formerly referred to as shaken baby syndrome) can be ruled out by an ophthalmologic exam for retinal hemorrhages and a noncontrast CT for subdural hematoma. Infants with abusive head trauma often do not exhibit external signs of abuse.
- An MRI can visualize white-matter changes associated with violent shaking and the extent

of intracranial and extracranial bleeds.

Treatment

- Document and photograph findings, including location; size; shape; color; and the nature of all lesions, bruises, or burns.
- Notify child protective services for evaluation of safety of the child in their current home.
- Hospitalize if necessary to stabilize injuries or to protect the child.
- Administer antibiotics and high-dose oral contraceptives for victims of sexual abuse.

WELL-CHILD CARE

ANTICIPATORY GUIDANCE

An important aspect of every well-child visit. Commonly discussed advice includes the following:

- Keep the water heater at <48.8°C (<120°F).
- Babies should sleep on their backs without any stuffed animals, toys, or bottles in the crib (to ↓ the risk for sudden infant death syndrome [SIDS]).
- Car safety seats should be rear facing and should be placed in the back of the car (seats can face forward if the child is >2 years of age and weighs >18 kg [>40 lb]).
- No solid foods should be given before 6 months of age; solid foods should then be introduced gradually and one at a time. Do not give cow's milk before 12 months of age (increases risk of iron-deficiency anemia).
- Syrup of ipecac (an emetic) is no longer routinely recommended for accidental poisoning. Poison control should be contacted immediately for assistance.
- Other guidance important to mention in a well-child visit includes the following:
  - Children should wear helmets when riding bicycles.
  - Parents should ensure that firearms are not loaded and are locked away.
  - Smoke detectors should be present and in working order.
  - Intake of sugar-sweetened drinks and juices is strongly discouraged; juice should be avoided before 12 months of age.
  - Safe sex education should be provided for adolescents.
  - Screen time should be limited for children, as hands-on learning is essential for children younger than 24 months.

KEY FACT

SIDS: Sudden infant death syndrome. Most common cause of unexplained death in children <1 year of age. Unknown pathogenesis.

BRUE: Brief resolved unexplained event. <1 minute in duration with no known cause. May present with an abrupt change in respiration, ↓ responsiveness, cyanosis, and change in muscle tone. No longer thought to be a precursor of SIDS.

Q

A mother presents with her previously healthy 3-month-old infant boy, stating that he has been increasingly difficult to rouse for the past 4 hours and has lost interest in feeding; she left the baby alone with her boyfriend while she ran errands. While en route to the hospital, the baby stopped breathing. PE is notable for occipital bruising. What is the most likely cause of this child's apnea?

HEARING AND VISION SCREENING

- Objective hearing screening (otoacoustic emissions and/or auditory brainstem response) for newborns before discharge is a standard of care. Children who fail these screening tests require further diagnostic workup.
- Objective hearing screening is indicated for children with a history of meningitis, TORCH infections, measles and mumps, and recurrent otitis media. The most common cause of childhood conductive hearing loss is repeated ear infections.
- The red reflex should be checked at birth. Leukocoria is the lack of a red reflex and can indicate the presence of retinoblastoma. It can also be an incidental finding in a baby's first photos.
- Vision screening to detect strabismus (ocular misalignment), amblyopia (suppression of retinal images in a misaligned eye, leading to permanent vision loss), and other conditions should be performed at all health visits in children <5 years of age.
- Strabismus is normal until 3 months of age; beyond 3 months of age, children should be evaluated by a pediatric ophthalmologist and may require corrective lenses, occlusion, and/or surgery to prevent amblyopia. Treatment of strabismus includes occluding the normal eye with an eye patch to strengthen the muscles and use of the abnormal eye.

KEY FACT

Leukocoria indicates retinoblastoma, congenital cataracts, or retinopathy of prematurity. All cases of leukocoria require immediate ophthalmologic workup.

CHILDHOOD VACCINATIONS

The Epidemiology chapter summarizes Centers for Disease Control and Prevention (CDC)–recommended vaccinations for the pediatric population. Contraindications and precautions in this population are as follows.

Contraindications:

- Severe allergy to a vaccine component or a prior dose of vaccine. Patients who have life-threatening allergies to eggs may receive measles, mumps, and rubella (MMR) and influenza vaccinations under observation. The physician should exercise caution in administering yellow fever vaccinations to those with egg allergies.
- Encephalopathy within 7 days of prior pertussis vaccination.
- Personal history of intussusception and SCID contraindications for the rotavirus vaccine.
- Live vaccines (rotavirus, oral polio vaccine, varicella, MMR, intranasal influenza, yellow fever) to be avoided in immunocompromised and pregnant patients (exception: HIV patients with CD4$^+$ cell count >200 copies/mm^3 may receive MMR and varicella).

Precautions:

- Current moderate to severe illness (with or without fever)
- Prior reactions to pertussis vaccine (fever >40.5°C [>104.9°F]), a shocklike state, persistent crying for >3 hours within 48 hours of vaccination, or seizure within 3 days of vaccination
- History of receiving IVIG in the past year

The following are not contraindications to vaccination:

- Mild illness and/or low-grade fever
- Current antibiotic therapy
- Prematurity—all vaccines should be given, based on the child's chronologic age, even if the child is premature

A

The most likely cause of this infant's apnea is abusive head trauma, which is most common in 3- to 4-month-old infants and presents early with nonspecific symptoms (lethargy, irritability, poor feeding, vomiting) and later with seizures or apnea. There is generally no reported history of head trauma. Subdural hematoma and edema account for most neurologic findings. In babies with abusive head trauma, there is a 50%–70% chance of prior abuse.

LEAD POISONING

Most exposure in children is caused by lead-contaminated household dust from lead paint. Screening should be routinely performed at 12 and 24 months of age for patients living in high-risk areas (pre-1970s homes or zip codes with high percentages of elevated blood lead levels). Universal screening is not recommended.

History/PE

- Children are usually asymptomatic. Children <6 years are most susceptible to the effects of lead because of an immature blood-brain barrier.
- Common symptoms include peripheral neuropathy (wrist and foot drop), cognitive impairment, colicky abdominal pain, constipation, headache, hyperactivity or apathy, and anorexia.
- Acute encephalopathy (usually with levels >70 µg/dL) is characterized by ↑ ICP, vomiting, confusion, seizures, and coma.

KEY FACT

New evidence has shown impaired intelligence and neurodevelopmental outcomes among children exposed to lead levels as low as 10 µg/dL.

Diagnosis

- The physician should do a fingerstick test as an initial screen at 1 or 2 years of age; if elevated, then a serum venous blood lead level should be obtained.

- CBC and peripheral blood smear show microcytic, hypochromic anemia and basophilic stippling (see Fig. 2.12-29). Sideroblastic anemia may also be present. Note that concurrent iron-deficiency anemia may also be present, as both lead poisoning and iron deficiency share similar risk factors.

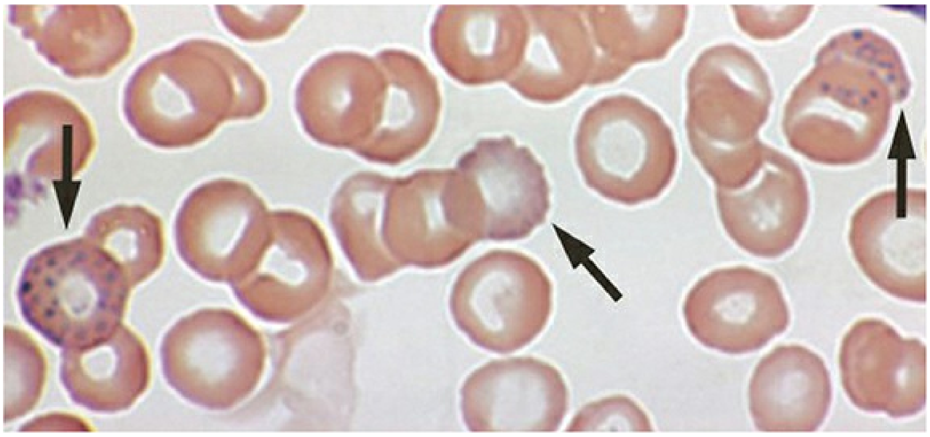
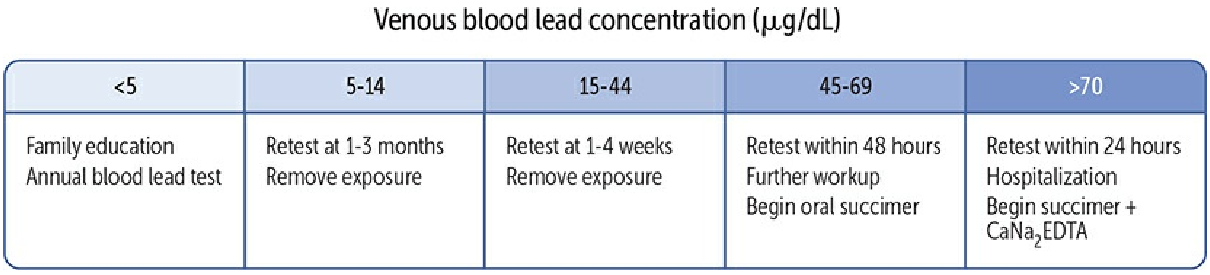


FIGURE 2.12-29. **Basophilic stippling *(arrows)* in lead poisoning.** (Reproduced courtesy of van Dijk HA, Fred HL. Images of memorable cases: case 81. Connexions Web site. December 3, 2008. Available at https://cnx.org/contents/MZa_Ph4e@4/Images-of-Memorable-Cases-Case.)

- X-ray of the abdomen may be useful in assessing for ingestion of objects containing lead.

Treatment

Blood lead levels (see Fig. 2-12-30):



Venous blood lead concentration (µg/dL)

<5	5-14	15-44	45-69	>70
Family education Annual blood lead test	Retest at 1-3 months Remove exposure	Retest at 1-4 weeks Remove exposure	Retest within 48 hours Further workup Begin oral succimer	Retest within 24 hours Hospitalization Begin succimer + CaNa$_2$EDTA

FIGURE 2.12-30. **Treatment based on venous blood lead levels.** (Reproduced with permission from USMLE-Rx.com.)

- <5 µg/dL: Family education and annual test of blood lead levels
- 5 to 14 µg/dL: Retest at 1 to 3 months; remove sources of lead
- 15 to 44 µg/dL: Retest within 1 to 4 weeks; remove sources of lead exposure
- 45 to 69 µg/dL: Retest within 48 hours, further workup (eg, x-ray of the abdomen, electrolytes), commencement of chelation therapy (oral succimer is recommended)
- >70 µg/dL: Retest within 24 hours; urgent evaluations, hospitalization, and chelation therapy (succimer + edetate calcium disodium [CaNa$_2$EDTA])

PERIANAL DERMATITIS

The commonly tested perianal dermatoses are listed in Table 2.12-32.

TABLE 2.12-32. **Perianal Dermatoses**

DIAGNOSIS	DESCRIPTION	TREATMENT
Irritant contact dermatitis	Most common in infants. Presents as erythematous rash that spares the skinfolds. Classically due to skin breakdown by exposure to urine or stool.	Topical barrier ointment (eg, zinc oxide, petrolatum)
Candida diaper dermatitis	Second most common in infants. Presents as beefy red, confluent plaques with satellite lesions. Does not spare the skinfolds.	Topical antifungal (eg, nystatin)
Perianal streptococcus	Occurs in school-aged children in addition to infants. Presents as a red, sharply demarcated perianal rash with associated pruritis and pain. May have blood-streaked stools or constipation from withholding stool due to pain. Diagnosis can be confirmed with perianal bacterial culture.	Oral β-lactam antibiotics

PIGMENTED LESIONS IN CHILDHOOD

The commonly tested lesions are listed in Table 2.12-33.

TABLE 2.12-33. **Pigmented Lesions in Childhood**

LESION	DESCRIPTION
Congenital melanocytic nevus	Benign proliferation of melanocytes with an increased density of hair follicles. They present as solitary hyperpigmented lesions with coarse hair (Image A). The melanocytes may enlarge during infancy; large lesions are often surgically removed due to increased risk of transformation to melanoma.
Congenital dermal melanocytosis (CDM) (Mongolian spot)	Multiple poorly circumscribed, nontender, flat, blue-gray patches that do not blanch (Image B). They are often located on the lower back and sacral region and fade spontaneously during childhood. More common in people of Asian and Black descent. Congenital dermal melanocytosis may be mistaken for bruises due to abuse; however, bruises are tender, show color variation, and fade quickly. Presence of CDM should be documented on initial evaluation.
Café au lait spots	Flat, hyperpigmented patches having "coffee with milk" appearance (Image C). Isolated spots are most often idiopathic/benign, but multiple spots may be associated with McCune-Albright syndrome and neurofibromatosis.

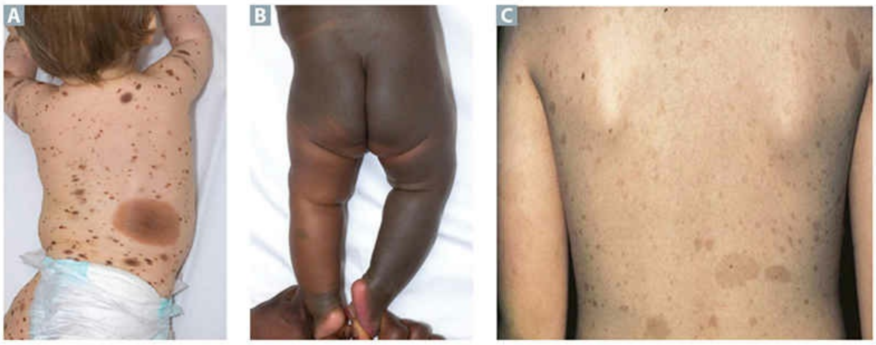


Image A reproduced with permission from Kinsler VA, O'Hare P, Jacques T, Hargrave D, Slater O. MEK inhibition appears to improve symptom control in primary NRAS-driven CNS melanoma in children. *Br J Cancer.* 2017;116(8):990-993. doi:10.1038/bjc.2017.49. Image B reproduced with permission from Thomas AC et al. Mosaic activating mutations in GNA11 and GNAQ are associated with phakomatosis pigmentovascularis and extensive dermal melanocytosis. *J Invest Dermatol.* 2016;136(4):770-778. doi:10.1016/j.jid.2015.11.027. Image C reproduced with permission from Khalil J, Afif M, Elkacemi H, et al. Breast cancer associated with neurofibromatosis type 1: a case series and review of the literature. *J Med Case Rep.* 2015;9:61 doi:10.1186/s13256-015-0533-8.

NOTES

HIGH-YIELD FACTS IN

PSYCHIATRY

Childhood and Adolescent Disorders
- ATTENTION-DEFICIT/HYPERACTIVITY
- AUTISM SPECTRUM DISORDER
- DISRUPTIVE BEHAVIORAL DISORDERS
- INTELLECTUAL DEVELOPMENTAL DISORDER/INTELLECTUAL DISABILITY
- TOURETTE SYNDROME
- SEPARATION ANXIETY DISORDER

Psychotic Disorders
- SCHIZOPHRENIA
- SCHIZOPHRENIFORM

Dissociative Disorders

Anxiety Disorders
- GENERALIZED ANXIETY DISORDER
- PANIC DISORDER
- PHOBIAS (SOCIAL AND SPECIFIC)

Obsessive-Compulsive Disorder and Related Disorders
- OBSESSIVE-COMPULSIVE DISORDER
- OBSESSIVE-COMPULSIVE–RELATED DISORDERS

Trauma and Stressor-Related Disorders
- POSTTRAUMATIC STRESS DISORDER

Neurocognitive Disorders
- DEMENTIA (MAJOR NEUROCOGNITIVE DISORDER)
- DELIRIUM

Mood Disorders
- MAJOR DEPRESSIVE DISORDER
- PERSISTENT DEPRESSIVE DISORDER (DYSTHYMIA)
- ADJUSTMENT DISORDER
- BIPOLAR AND RELATED DISORDERS

Personality Disorders

Substance Use Disorders
- ALCOHOL USE DISORDER
- MANAGEMENT OF DRUG WITHDRAWAL

Eating Disorders
- ANOREXIA NERVOSA
- BULIMIA NERVOSA

Sexual Disorders
- SEXUAL CHANGES WITH AGING
- PARAPHILIC DISORDERS
- GENDER DYSPHORIA
- SEXUAL DYSFUNCTION

Sleep Disorders
- PRIMARY INSOMNIA
- PRIMARY HYPERSOMNIA
- NARCOLEPSY
- SLEEP APNEA
- CIRCADIAN RHYTHM SLEEP DISORDER

Somatic Symptom and Related Disorders
- SOMATIC SYMPTOM DISORDER
- ILLNESS ANXIETY DISORDER
- CONVERSION DISORDER

Factitious Disorders and Malingering

Sexual and Physical Abuse
- SEXUAL ASSAULT

Suicidality

CHILDHOOD AND ADOLESCENT DISORDERS

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

A persistent pattern of excessive inattention and/or hyperactivity/impulsivity. Typically presents between 3 and 13 years of age; more common in males; often shows a familial relationship

History/PE

Attention-deficit/hyperactivity disorder (ADHD) presents with core symptoms that can be divided into the following two categories:

- **Inattention:** Exhibits a poor/short attention span in schoolwork/play; displays poor attention to detail or careless mistakes; has difficulty following instructions or finishing tasks; is forgetful and easily distracted
- **Hyperactivity/impulsivity:** Fidgets; leaves seat in classroom; runs around inappropriately; cannot play quietly; talks excessively; does not wait for their turn; interrupts others

Diagnosis

- Symptoms must be present and cause an impairment in functioning for ≥6 months in at least two independent settings (eg, home and school).
- Age <17 years: Diagnosis requires six or more symptoms from either category of core

symptoms (inattention and/or hyperactivity/impulsivity)

- Age ≥17 years: Diagnosis requires five or more symptoms from either category of core symptoms
- Symptoms must be present before 12 years of age
- Alternative causes of inattention and/or hyperactivity must be considered (such as substance abuse, organic reasons [eg, lead toxicity], hearing/visual impairment, thyroid disorders, sleep disorders, absence seizures)

Treatment

Four to five years of age:

- **Best initial treatment:** Behavior therapy. The physician can add medication if behaviors do not improve.

Six years of age or older:

- **Best initial treatment:** Pharmacologic therapy + behavior therapy
- **First line:** Central nervous system (CNS) stimulants (eg, methylphenidate, dextroamphetamine, amphetamine salts [dextroamphetamine and amphetamine combo])
- Adverse effects: Weight loss (↓ appetite), insomnia, anxiety, irritability, headache, tic exacerbation, and ↓ growth velocity (normalizes when medication is stopped)
- Because of stimulants' potential for causing weight loss, it is recommended to give them after meals

KEY FACT

Use of stimulants is contraindicated for individuals with illicit substance abuse at risk for addiction and those whose parent/legal guardian is against their use.

- Alternatives: Nonstimulants
  - Atomoxetine (norepinephrine reuptake inhibitor; second-line treatment): Can be tried first because of the negative side-effect profile of CNS stimulants
  - Third-line treatments: clonidine/guanfacine (α_2-agonist), bupropion, and tricyclic antidepressants (TCAs)

All ages: Continuation of regular diet. Sugar and food additives are not considered etiologic factors.

KEY FACT

Children must exhibit ADHD symptoms in two or more settings (eg, home and school).

AUTISM SPECTRUM DISORDER

Developmental disorder characterized by impairments in two major domains: (1) social interaction and communication and (2) repetitive/restricted behavior, interests, or activities. Autism spectrum disorder (ASD) is more common in males. Severity is based on the level of support required for each domain. The *Diagnostic and Statistical Manual of Mental*

Disorders (*DSM*)-*5* does not distinguish among the pervasive developmental disorders.

History/PE

- Deficits in social interaction and communication: Reduced interest in socialization, reduced empathy, inability to form relationships, impaired language development, inability to understand social cues, poor eye contact
  - Prognosis is best determined by language development because its development is based on social interaction
- Restricted/repetitive patterns of behavior, interests, or activities: Highly fixated or restricted interests, inflexibility to change, hand flapping or other stereotypies, increased/decreased response to sensory input (eg, indifference to temperature, excessive touching/smelling, adverse responses to sounds)
- Symptoms must impair function (eg, academic, social)
- Symptoms must be present in the early developmental period (typically <3 years of age)
- Conditions that produce symptoms suggestive of ASD must be excluded:
  - Intellectual disability or global developmental delay
  - Hearing impairment: Ruled out with audiometry before making diagnosis
  - Selective mutism: Refusal to speak only in social situations
  - Rett syndrome: Similar to ASD; X-linked disorder characterized by marked physical and psychomotor regression at approximately 6 months of age after normal development. Predominantly seen in females; patients have classic hand-wringing movements
  - Fragile X syndrome: X-linked dominant disorder caused by hypermethylation of *FMR1* gene; most common cause of *inherited* intellectual disability and autism; presents with the following characteristics: macro-orchidism, long face, prominent jaw and forehead, high arched palate, large and everted ears, autism, connective tissue laxity, and /or mitral valve prolapse

Treatment

- Intensive special education, behavioral management (specifically applied behavior analysis therapy), and symptom-targeted medications (eg, stimulants or α_2-agonists for ADHD; neuroleptics for aggression and mood instability; selective serotonin reuptake inhibitors [SSRIs] for stereotypical behavior, anxiety, and mood)
- Family support and counseling—crucial components of treatment

KEY FACT

In patients with ASD, think about associated congenital conditions, such as Rett syndrome, tuberous sclerosis, and fragile X syndrome.

DISRUPTIVE BEHAVIORAL DISORDERS

Includes conduct disorder, oppositional defiant disorder (ODD), and disruptive mood dysregulation disorder (DMDD). More common in males and in patients with a history of abuse. Psychiatric comorbidities are common (eg, post-traumatic stress disorder [PTSD], depression, substance abuse, somatoform conditions, personality disorders).

History/PE

- **ODD:** A pattern of negative, defiant, disobedient, and hostile behavior toward authority figures (eg, losing temper, arguing) for ≥6 months. May progress to conduct disorder.
- **Conduct disorder:** A repetitive, persistent pattern of violating the basic rights of others or age-appropriate societal norms/rules for ≥1 year in children <18 years of age. Behaviors can be aggressive (eg, rape, robbery, animal cruelty) or nonaggressive (eg, destruction of property, stealing, lying, running away, and truancy). After 18 years of age, conduct disorder is considered antisocial personality disorder.
- **DMDD:** A pattern of severe, recurrent verbal (eg, screaming) or behavioral (eg, physical aggression) outbursts that are out of proportion to the situation and a persistently irritable or angry mood between outbursts.
  - Symptoms must occur for ≥1 year; they may progress to depression in adulthood.
  - DMDD should not be diagnosed before 6 years of age or after 18 years of age.

Treatment

Psychotherapy is the first-line treatment for all disruptive behavioral disorders.

KEY FACT

Conduct disorder is diagnosed in **C**hildren. **A**ntisocial personality disorder is diagnosed in **A**dults.

INTELLECTUAL DEVELOPMENTAL DISORDER/INTELLECTUAL DISABILITY

Disorder of cognitive, social, and practical functioning. Associated with male sex, chromosomal abnormalities, congenital infections, teratogens (including alcohol/illicit substances), and inborn errors of metabolism. Most often no identifiable cause is found in most patients with intellectual disability.

History/PE

- Patients have deficiencies in multiple domains as follows:
  - **Intellectual deficits:** Poor reasoning, problem solving, planning, and performance on standardized testing
  - **Adaptive functioning deficits:** Poor hygiene, social functioning, activities of daily living (ADLs)
- **Onset:** During developmental period (<18 years of age)
- **Severity of intellectual disability:** Determined by level of support required to address impaired adaptive functioning (IQ cutoffs for severity are no longer used with the *DSM-5*)
  - Mild (independent in ADLs); moderate (some teaching and support for ADLs); severe (significant support for ADLs); profound (dependent on support for all ADLs)
- **Differential diagnosis:** Specific learning disorder (reading, math, or writing skills that are significantly lower than expected for age and intelligence)
  - Reading disorder is the most common

Treatment

- **Primary prevention:** Educating the public about possible causes of intellectual disability

and providing optimal prenatal screening and care to pregnant patients
- **Treatment measures:** Family counseling and support, speech and language therapy, occupational/physical therapy, behavioral intervention, educational assistance, and social skills training
- **Learning disorder:** Remedial therapy directed toward patient's deficiency

KEY FACT

- Down syndrome (trisomy 21): The most common chromosomal cause of intellectual disability
- Fetal alcohol syndrome (FAS): The most common preventable cause of intellectual disability
- Fragile X syndrome: The most common inherited form of intellectual disability

TOURETTE SYNDROME

Disorder characterized by both motor and vocal tics. More common in males; shows a genetic predisposition. Associated with ADHD, learning disorders, and obsessive-compulsive disorder (OCD). Symptoms can be temporarily suppressed with effort or exacerbated by stress and fatigue.

History/PE

Symptoms begin <18 years of age and cause social or occupational impairment.

Diagnosis

Diagnosis requires the following:

- Multiple motor tics (eg, blinking, grimacing)
- One or more vocal tics (eg, grunting, coprolalia, echolalia, throat clearing, coughing)
- Tics present for >1 year
- Tics recurrent (occur many times per day and/or nearly every day)

Treatment

Best initial treatment: Behavior therapy; habit reversal therapy is most effective. If behavior therapy fails or tics are severe/disabling, the next step is pharmacologic management.

- **Antidopaminergic agents:**
  - **Dopamine-depleting agents** (eg, tetrabenazine [vesicular monoamine transporter (VMAT)-2 inhibitor; results in ↓ uptake of monoamines]): Preferred over dopamine-blocking agents; does not cause tardive dyskinesia (TD)
  - **Dopamine-blocking agents:** Antipsychotics (eg, fluphenazine, risperidone, haloperidol, pimozide)
  - **For severe, refractory tics:** Typical antipsychotics (eg, haldol, pimozide)
- **α_2-agonists** (eg, clonidine, guanfacine): Less effective at tic reduction; more favorable side-effect profile

Differential Diagnosis

Persistent (chronic) tic disorder consisting of either motor or vocal tics (but not both) which last >1 year.

KEY FACT

Coprolalia = Repetition of obscene words
Echolalia = Repetition of words spoken by others

SEPARATION ANXIETY DISORDER

Disorder characterized by fear of separation from an attachment figure (eg, parent) or home. Separation anxiety normally begins at about 1 year of age and peaks at 18 months. Considered pathologic if it becomes extreme or persists. May be precipitated by a stressful event.

History/PE

Fear of separation from an attachment figure or home lasting for ≥4 weeks in children or ≥6 months in adults. May present as complaints of somatic symptoms to avoid school or work.

Diagnosis

Excessive fear of separation from attachment figures and three of the following:

- Separation that leads to extreme distress
- Separation that leads to social, academic, or occupational dysfunction
- Excessive worry about losing attachment figure
- Reluctance to leave home, sleep alone, or be alone
- Nightmares of separation
- Physical symptoms (eg, a stomachache) when separated

Treatment

Cognitive-behavioral therapy (CBT), family therapy, SSRIs as an adjunct to therapy.

PSYCHOTIC DISORDERS

SCHIZOPHRENIA

Disorder of thought process characterized by psychotic symptoms that are further divided into positive symptoms (hallucinations, delusions, disorganized thought/behavior) and negative symptoms (flat affect, social withdrawal, apathy).

- **Epidemiology:** Prevalence is ~1% (males > females). Peak onset is earlier in males (18–25 years of age) than in females (25–35 years of age). Schizophrenia in first-degree relatives ↑ risk. Up to 50% of patients attempt suicide; 10% of patients with schizophrenia complete suicide.
- **Etiology:** Unknown. Theories focus on neurotransmitter abnormalities such as dopamine dysregulation (frontal hypoactivity and limbic hyperactivity) and brain abnormalities on CT and MRI (enlarged ventricles and ↓ cortical volume).

KEY FACT

Psychosis (hallucinations and/or delusions without insight) ≠ schizophrenia. Differential diagnosis must also include organic diseases, other psychiatric illnesses, and substance-induced psychosis.

History/PE

- Schizophrenia presents with chronic or recurrent psychosis, disorganization, and/or negative symptoms.
- Cognitive impairment in multiple areas (eg, processing speed, working memory, attention, social cognition) may be present.
- Mood and anxiety symptoms are common.

Diagnosis

Requires two or more of the following symptoms for ≥6 months with social or occupational dysfunction; at least one of the symptoms must be hallucinations, delusions, or disorganized speech:

- Hallucinations (most often auditory)
- Delusions
- Disorganized speech
- Disorganized or catatonic behavior
- **Negative symptoms:** Flattened affect, social withdrawal, anhedonia, apathy, ↓ emotion; may mimic depression

MNEMONIC

***Five As of schizophrenia diagnosis**—**A**ffect (flat), **A**volition, **A**sociality, **A**nhedonia, **A**pathy*

SCHIZOPHRENIFORM

Disorder of thought process. Presentation similar to schizophrenia, but psychotic symptoms are present for 1 to 6 months only.

See Table 2.13-1 for the differential diagnosis of psychosis.

TABLE 2.13-1. **Differential Diagnosis of Psychosis**

DISORDER	DURATION/CHARACTERISTICS
Psychotic disorders	Brief psychotic disorder: 1 day to 1 month Schizophreniform disorder: 1–6 months *Note:* Both present similarly to schizophrenia but are differentiated by duration of illness; can be preceded by stressor(s), are less likely to have negative symptoms, and have a better lifetime prognosis than schizophrenia Schizophrenia: >6 months Schizoaffective disorder: Psychosis + mood disorder (mania or depression); Requires history/presence of: ▪ Psychosis + mood episode AND ▪ Psychosis for ≥2 weeks without mood episode
Personality disorders	Schizotypal: "Magical thinking" Schizoid: "Loners"
Delusional disorder	Persistent delusions (often nonbizarre) without disorganized thought process, hallucinations, or negative symptoms of schizophrenia; subtypes are jealous, paranoid, somatic, erotomanic, or grandiose Symptoms must be present ≥1 month Day-to-day functioning is mostly unaffected Folie à deux: A shared delusion (commonly between parent and child); the best course of action is to separate the patient pair and treat individually

Prognosis

Better prognosis:

- Acute onset with positive manifestations (hallucinations and delusions)
- No family history

- Rapid symptom resolution with treatment initiation

Poor prognosis:

- Symptoms arise before 13 years of age
- Insidious course with depressive states
- Developmental delay; timid, introverted, and uncommunicative before manifesting symptoms

KEY FACT

In addition to psychotic symptoms, a patient must have mood symptoms present the majority of the time for a physician to differentiate schizoaffective disorder from schizophrenia.

KEY FACT

Terms used to describe components of psychosis are as follows:

- Delusion: A fixed false idiosyncratic belief
- Hallucination: Perception without an existing external stimulus
- Illusion: Misperception of an actual external stimulus

Treatment

- Treatment is usually lifelong and often involves a combination of medications, psychotherapy, social skills training, and coordinated specialty care services.
- Pharmacologic intervention with antipsychotic medications can be used to treat the acute symptoms of psychosis, as well as for long-term management and prevention of symptoms (see Table 2.13-2).

TABLE 2.13-2. Antipsychotic Medications

DRUG CLASS	MECHANISM	EXAMPLES	INDICATIONS	ADVERSE EFFECTS
Typical antipsychotics	D_2 antagonist (high potency)	Haloperidol[a], fluphenazine[a]	Psychotic disorders, acute agitation, acute mania, Tourette syndrome Thought to be more effective for positive symptoms of schizophrenia If compliance is a major issue, the physician can consider antipsychotics available in long-acting depot form[a]	EPSs (see Table 2.13-3) > anticholinergic symptoms (dry mouth, urinary retention, constipation) QTc prolongation and torsades de pointes, especially with IV haloperidol Neuroleptic malignant syndrome
	D_2 antagonist (low potency)	Thioridazine, chlorpromazine	Same as high potency	Anticholinergic > EPSs More sedating Greater risk for orthostatic hypotension Thioridazine causes QTc prolongation and irreversible retinal pigmentation
Atypical antipsychotics	D_2 antagonist, 5-HT_{2A} antagonist	Risperidone[a], quetiapine, olanzapine[a], paliperidone[a], ziprasidone, clozapine	First-line treatment for schizophrenia, given fewer EPSs and anticholinergic effects Clozapine is reserved for severe treatment resistance and severe tardive dyskinesia	↓ EPSs (due to 5- HT_{2A} antagonism) Weight gain, dyslipidemia, type 2 DM, somnolence, sedation, and QTc prolongation (ziprasidone); hyperprolactinemia (risperidone) Clozapine can cause agranulocytosis; its use requires weekly CBC monitoring during first 6 months
	D_2 partial agonist, 5-HT_{1A} partial agonist, 5-HT_{2A} antagonist	Aripiprazole[a]	Same as other atypicals, except it does not cause hyperprolactinemia due to its ability to act as a D_2 receptor agonist under hypodopaminergic conditions and as a D_2 receptor antagonist during hyperdopaminergic conditions	

[a] Also available as a long-acting depot injection. *CBC*, Complete blood cell count; *DM*, diabetes mellitus; *EPS*, Extrapyramidal symptom; *HT*, hydroxytryptamine; *IV*, intravenous.

KEY FACT

In those with poor medication adherence or noncompliance, depot (injectable) is preferred because they are longer-acting medications.

KEY FACT

Atypical antipsychotics (olanzapine, risperidone, quetiapine) are preferred to typical antipsychotics (haloperidol, thioridazine, chlorpromazine), given fewer EPSs and anticholinergic effects.

KEY FACT

Resistance is considered when a minimum of two drugs have been attempted previously without improvement of symptoms.

Q

A 24-year-old woman presents to the clinic. She has been “hearing voices” and has isolated herself from her friends and family. She first noticed the voices about 2 months ago when she was feeling sad and reported sleeping poorly. She reports that her mood has since improved and denies any current sleep disturbances but is still hearing the voices. What is her most likely diagnosis?

- Supportive psychotherapy, training in social skills, vocational rehabilitation, and illness education may help. In particular, family psychoeducation/therapy decreases the risk for relapse.
- Negative symptoms may be more difficult to treat than positive symptoms; atypical antipsychotics are the drug of choice.
- Catatonia (awkward posturing, mutism, and immobility) may be seen in severe disease; this can be treated with benzodiazepine challenge and electroconvulsive therapy (ECT). Find a description of ECT in the Major Depressive Disorder section later in this chapter.

A

This patient most likely has schizoaffective disorder, which is characterized by psychosis and intermittent mood symptoms. The diagnosis requires (1) psychotic symptoms AND mood symptoms and (2) at least 2 weeks when psychotic symptoms are present WITHOUT mood symptoms. Patients often have chronic psychotic symptoms, even after mood symptoms have resolved.

TABLE 2.13-3. **Extrapyramidal Symptoms and Treatment**

SUBTYPE	DESCRIPTION	TIME OF ONSET	TREATMENT
Acute dystonia	Prolonged, painful tonic muscle contraction or spasm (eg, torticollis, oculogyric crisis)	Hours	Anticholinergics (benztropine or diphenhydramine) for acute therapy Patients who are prone to dystonic reactions may need regular prophylactic dosing (eg, benztropine)
Akathisia	Subjective/objective restlessness that is perceived as being distressing	Weeks	↓ dose of neuroleptic; β-blockers (propranolol) Benzodiazepines (lorazepam) or anticholinergics (benztropine)
Dyskinesia	Pseudo-parkinsonism (eg, tremor, shuffling gait, cogwheel rigidity)	Weeks	↓ dose of neuroleptic or discontinue (if tolerated) Anticholinergics (benztropine) or dopamine agonist (amantadine)
Tardive dyskinesia	Stereotypic, involuntary, painless oral-facial movements Probably from dopamine receptor sensitization from chronic dopamine blockade Often irreversible (50%)	Months	Discontinue or ↓ dose of neuroleptic; possibly change neuroleptic (eg, to clozapine or quetiapine) Anticholinergics or ↓ neuroleptic dose may initially worsen tardive dyskinesia If discontinuing or ↓ neuroleptic dose is ineffective, try valbenazine or deutetrabenazine
Neuroleptic malignant syndrome	Fever, muscle rigidity, autonomic instability, elevated creatine kinase and white blood cells, delirium	Any time	Discontinue medication; provide supportive care in the intensive care unit (ICU); administer dantrolene or bromocriptine

MNEMONIC

Evolution of extrapyramidal symptoms—

4 and A

4 hours: **A**cute dystonia
4 days: **A**kinesia

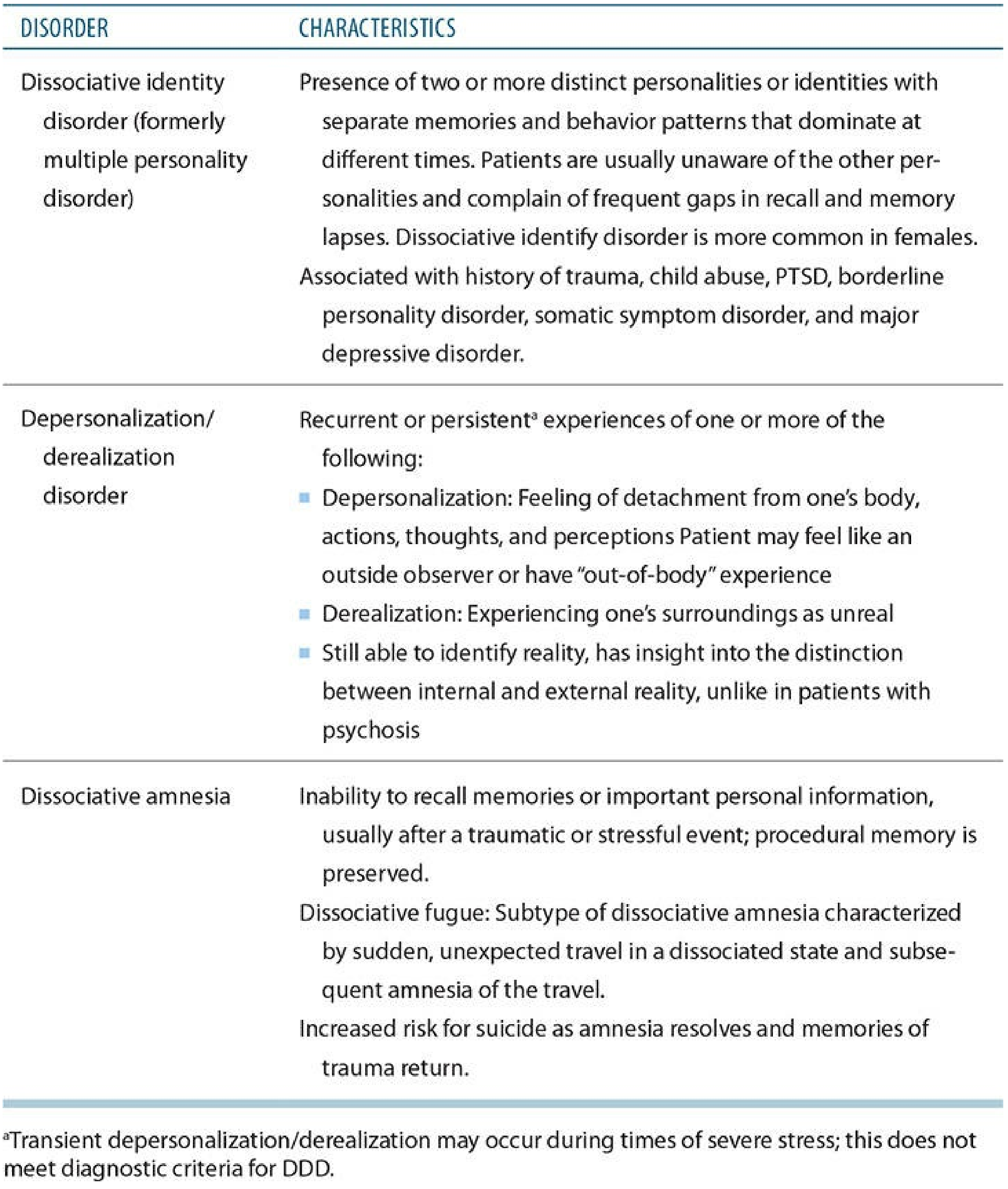
4 weeks: **A**kathisia
4 months: Tardive dyskinesia (often permanent)

DISSOCIATIVE DISORDERS

Includes dissociative identity disorder, depersonalization/derealization disorder, and dissociative amnesia. Symptoms are not better explained by substance use, another medical condition, or another mental disorder.

See Table 2.13-4 for an overview of the dissociative disorders.

TABLE 2.13-4. Overview of Dissociative Disorders



DISORDER	CHARACTERISTICS
Dissociative identity disorder (formerly multiple personality disorder)	Presence of two or more distinct personalities or identities with separate memories and behavior patterns that dominate at different times. Patients are usually unaware of the other personalities and complain of frequent gaps in recall and memory lapses. Dissociative identify disorder is more common in females. Associated with history of trauma, child abuse, PTSD, borderline personality disorder, somatic symptom disorder, and major depressive disorder.
Depersonalization/derealization disorder	Recurrent or persistent[a] experiences of one or more of the following: ▪ Depersonalization: Feeling of detachment from one's body, actions, thoughts, and perceptions Patient may feel like an outside observer or have "out-of-body" experience ▪ Derealization: Experiencing one's surroundings as unreal ▪ Still able to identify reality, has insight into the distinction between internal and external reality, unlike in patients with psychosis
Dissociative amnesia	Inability to recall memories or important personal information, usually after a traumatic or stressful event; procedural memory is preserved. Dissociative fugue: Subtype of dissociative amnesia characterized by sudden, unexpected travel in a dissociated state and subsequent amnesia of the travel. Increased risk for suicide as amnesia resolves and memories of trauma return.

[a] Transient depersonalization/derealization may occur during times of severe stress; this does not meet diagnostic criteria for DDD.

Treatment

- **Best initial treatment:** Psychotherapy
- Appropriate pharmacologic treatment (eg, SSRIs) can be added to address comorbidities (eg, depression, anxiety, substance abuse, PTSD)

ANXIETY DISORDERS

GENERALIZED ANXIETY DISORDER

Uncontrollable, excessive anxiety or worry about multiple topics that leads to significant impairment or distress.

History/PE

Clinical onset is usually in the early 20s. Generalized anxiety disorder (GAD) is more common in females.

Diagnosis

- GAD is diagnosed when excessive anxiety or worry about multiple activities is experienced on most days for ≥6 months.
- Symptoms of anxiety/worry are associated with three or more somatic symptoms (only one required in children): restlessness, easy fatigue, difficulty concentrating, irritability, muscle tension, sleep disturbances.
- Symptoms cause a clinically significant impairment (eg, social, occupational).
- Disturbances are not caused by substances (eg, drug of abuse [eg, cocaine], medication [eg, amphetamines]).
- Disturbance is not better explained by another psychiatric disorder (eg, excessive worry about panic attacks).

Treatment

- **Best initial treatment (first-line):** Psychotherapy (CBT, applied relaxation, biofeedback) + SSRIs (eg, fluoxetine, sertraline, escitalopram) or serotonin norepinephrine reuptake inhibitors (SNRIs, eg, venlafaxine, duloxetine). See Table 2.13-5.

TABLE 2.13-5. Anxiolytic Medications

DRUG CLASS	INDICATIONS	ADVERSE EFFECTS
SSRIs (eg, fluoxetine, sertraline, paroxetine, citalopram, escitalopram)	First-line treatment for GAD, OCD, panic disorder	Nausea, GI upset, somnolence, sexual dysfunction, agitation
SNRIs (eg, venlafaxine, duloxetine)	First-line treatment for GAD	Hypertension, stimulant effects
5-HT partial agonist (eg, buspirone)	Second-line treatment for GAD, social phobia Used if sexual dysfunction experienced with SSRIs	Headaches, dizziness, nausea No tolerance, dependence, or withdrawal
β-Blocker (propranolol)	Performance-only social anxiety disorder	Bradycardia, hypotension
Benzodiazepines (eg, clonazepam, alprazolam)	Anxiety (short-term), insomnia, alcohol withdrawal, muscle spasm, night terrors, sleepwalking	↑ sleep duration; risk for abuse, tolerance, and dependence; disinhibition in young or older patients; confusion Abruptly stopping a short-acting benzodiazepine (eg, alprazolam) can result in seizures

GAD, Generalized anxiety disorder; *GI*, gastrointestinal; *OCD*, obsessive-compulsive disorder.

- **Alternative treatment (second-line):** Buspirone, TCAs, benzodiazepines (short-term treatment).

MNEMONIC

The diagnosis of GAD in an adult requires the presence of three or more of the Worry* WARTS *symptoms:

Wound up (irritability)
Worn out (fatigue)
Absent-mindedness (difficulty concentrating)
Restlessness
Tension in muscles
Sleep disturbance

KEY FACT

Like SSRIs, buspirone should not be used in conjunction with monoamine oxidase inhibitors. (See Tables 2.13-5 and 2.13-11.)

PANIC DISORDER

Characterized by recurrent, unexpected periods of intense fear that last for several minutes and cause excessive worry about having another panic attack.

History/PE

- Recurrent episodes of intense fear and discomfort. Symptoms usually last ≤30 minutes.
- Associated with agoraphobia, increased risk of suicide.
- More common in females; may occur at any age. There is a strong genetic disposition.

Diagnosis

- **Panic attacks:** Discrete periods of intense fear or discomfort in which four or more of the following symptoms develop abruptly and peak within 10 minutes:
  - Tachycardia or palpitations, diaphoresis, chest pain, shortness of breath, nausea, trembling, dizziness, fear of dying or "going crazy," depersonalization, hot flashes, chills or heat sensation, paresthesia
  - Increased sensitivity to lactate infusion, which may precipitate an attack in the susceptible
- **Panic disorder:**
  - Recurrent, unexpected panic attacks
  - Attacks followed by ≥1 month of at least one of the following
    - Persistent worry/concern of having additional attacks
    - Maladaptive change in behavior (eg, avoidance of unfamiliar situations)
    - Worry about consequences of attack (eg, losing control)
    - Not explained by substances, medications, or another medical condition

KEY FACT

Differential diagnosis for panic disorders:

- Medical conditions: Angina, myocardial infarction (MI), arrhythmias, hyperthyroidism, pheochromocytoma, hypoglycemia
- Psychiatric conditions: Substance-induced anxiety, GAD, PTSD

Treatment

- See Table 2.13-5 for medications.
- **Acute, initial treatment:** Benzodiazepines (eg, clonazepam). Long-term use should be avoided due to concerns of potential dependence and abuse. Benzodiazepines should be tapered as soon as long-term treatment is effective.
- **Long-term treatment:** SSRIs (eg, sertraline).
- **Psychotherapy:** CBT; higher rates of response and sustained effects compared with placebo and pharmacotherapy alone

PHOBIAS (SOCIAL AND SPECIFIC)

Disorders characterized by excessive fear that is unreasonable and stimulated by the presence or anticipation of a specific object or situation. Patients recognize the fear is excessive. Symptoms are persistent, usually lasting ≥6 months.

History/PE

- **Social anxiety disorder:** Presents with excessive fear of criticism, humiliation, and embarrassment in multiple situations requiring social interaction. Patients may have anxiety in anticipation of the event, palpitations and sweating during the event, and they may avoid triggers (eg social events, parties, school).
  - **Performance-only subtype:** Symptoms provoked only by performance situations (eg, public speaking, test taking, sexual intercourse).
- **Specific phobia:** Excessive anxiety and fear provoked by exposure to a feared object or situation (eg, animals, heights, airplanes). Most cases begin in childhood.

- **Agoraphobia:** Fear/anxiety of developing paniclike symptoms in two or more situations from which it may be difficult to escape or get help, resulting in avoidance of those situations. Patients may become completely confined to the home. Agoraphobia is associated with panic disorder.

KEY FACT

Agoraphobia is defined as fear of being alone in public places. Literally translated, it means "fear of the marketplace."

Treatment

- **Social anxiety disorder:** Both CBT and SSRIs are first line, and the choice of treatment is dependent on patient preference. CBT involves desensitization through incremental exposure to the feared object or situation along with relaxation techniques. Second-line treatment includes benzodiazepines (if no history of substance use disorder) or phenelzine (if patient has a history of or risk factors for substance use disorder).
  - **Performance-only subtype:** First-line treatment with β-blockers (eg, propranolol) before the event or as needed. Second-line treatment includes CBT, benzodiazepines, and/or SSRIs.
- **Specific phobia:** First-line treatment is CBT. Second-line treatment includes SSRIs, benzodiazepines.
- **Agoraphobia:** CBT, SSRIs.

KEY FACT

In patients with a history of substance abuse, benzodiazepines should be avoided due to their high potential for addiction.

OBSESSIVE-COMPULSIVE DISORDER AND RELATED DISORDERS

OBSESSIVE-COMPULSIVE DISORDER

Characterized by obsessions and/or compulsions that lead to significant distress and dysfunction in social or personal areas. Compulsions are typically time-consuming, often requiring >1 hour daily. OCD typically presents in late adolescence or early adulthood; prevalence is equal in male and female patients. It is often chronic and difficult to treat.

KEY FACT

Abnormalities on brain imaging are common in patients with OCD, specifically in the orbitofrontal cortex and basal ganglia. The cortico-striato–thalamo-cortical (CSTC) circuits have been implicated in the pathophysiology of the disorder.

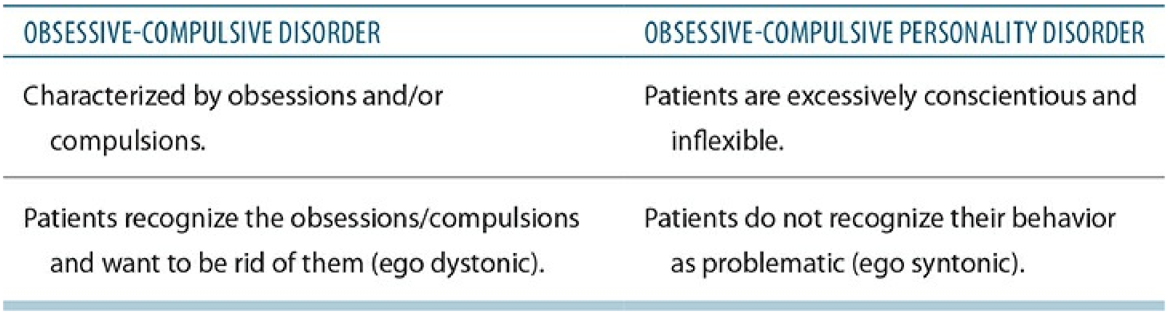
KEY FACT

Many patients with OCD initially present to a non-psychiatrist (eg, they may consult a dermatologist with a skin complaint secondary to overwashing their hands).

History/PE

- **Obsessions:** Persistent, unwanted, and intrusive ideas, thoughts, impulses, or images that lead to marked anxiety or distress (eg, fear of contamination, fear of harming oneself or loved ones)
- **Compulsions (or rituals):** Repeated mental acts or behaviors that neutralize anxiety from obsessions (eg, handwashing, elaborate rituals for ordinary tasks, counting, excessive checking)
- Patients recognize their behaviors as excessive and irrational (vs obsessive-compulsive personality disorder [OCPD]; see Table 2.13-6)

TABLE 2.13-6. **Obsessive-Compulsive Disorder vs Obsessive-Compulsive Personality Disorder**



OBSESSIVE-COMPULSIVE DISORDER	OBSESSIVE-COMPULSIVE PERSONALITY DISORDER
Characterized by obsessions and/or compulsions.	Patients are excessively conscientious and inflexible.
Patients recognize the obsessions/compulsions and want to be rid of them (ego dystonic).	Patients do not recognize their behavior as problematic (ego syntonic).

- Patients wish they could get rid of obsessions and/or compulsions

Treatment

- **Best initial treatment:** SSRIs (high dose)
    - **Alternative:** Clomipramine (TCA)
- CBT using exposure and desensitization relaxation techniques
- Patient education is imperative

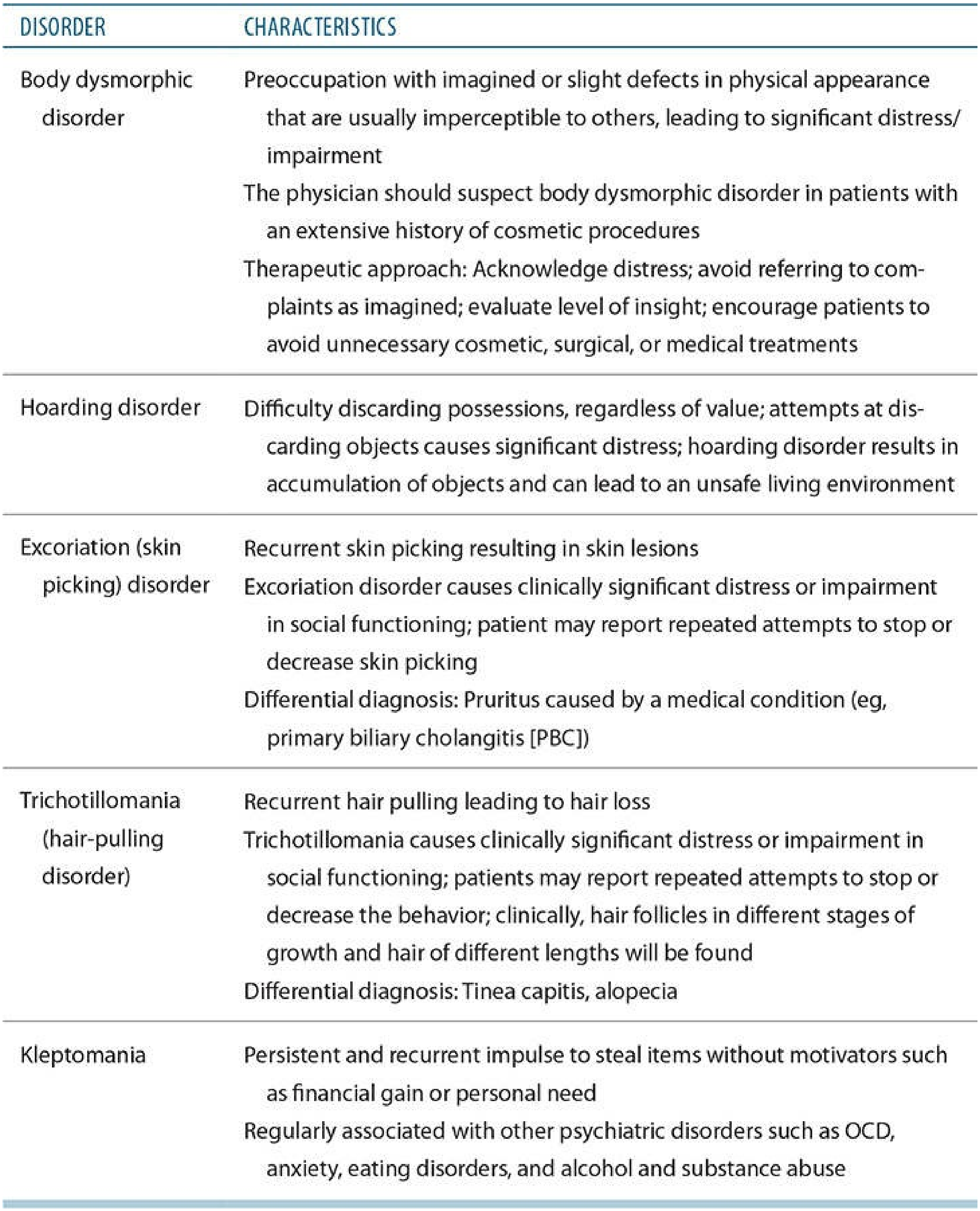
Q

A 22-year-old man presents to a physician’s office. He frequently washes his hands, refuses to sit on chairs in public places, and will not use public transportation for fear of contracting diseases. He does not think his behaviors are abnormal, nor does he think his behaviors interfere with his daily activities. What is the diagnosis?

OBSESSIVE-COMPULSIVE–RELATED DISORDERS

Obsessive-compulsive-related disorders are characterized by unwanted, intrusive, recurrent, and persistent thoughts, urges, or images, as well as repetitive behaviors or mental acts in response to those preoccupations. Some obsessive-compulsive–related disorders are primarily body-focused (eg, hair pulling, skin picking) with repeated attempts to decrease or stop the behaviors. Others involve mental acts that an individual feels driven to perform in response to an obsession or according to a rigid set of self-defined “rules” (see Table 2.13-7).

TABLE 2.13-7. **Obsessive-Compulsive–Related Disorders**



DISORDER	CHARACTERISTICS
Body dysmorphic disorder	Preoccupation with imagined or slight defects in physical appearance that are usually imperceptible to others, leading to significant distress/impairment The physician should suspect body dysmorphic disorder in patients with an extensive history of cosmetic procedures Therapeutic approach: Acknowledge distress; avoid referring to complaints as imagined; evaluate level of insight; encourage patients to avoid unnecessary cosmetic, surgical, or medical treatments
Hoarding disorder	Difficulty discarding possessions, regardless of value; attempts at discarding objects causes significant distress; hoarding disorder results in accumulation of objects and can lead to an unsafe living environment
Excoriation (skin picking) disorder	Recurrent skin picking resulting in skin lesions Excoriation disorder causes clinically significant distress or impairment in social functioning; patient may report repeated attempts to stop or decrease skin picking Differential diagnosis: Pruritus caused by a medical condition (eg, primary biliary cholangitis [PBC])
Trichotillomania (hair-pulling disorder)	Recurrent hair pulling leading to hair loss Trichotillomania causes clinically significant distress or impairment in social functioning; patients may report repeated attempts to stop or decrease the behavior; clinically, hair follicles in different stages of growth and hair of different lengths will be found Differential diagnosis: Tinea capitis, alopecia
Kleptomania	Persistent and recurrent impulse to steal items without motivators such as financial gain or personal need Regularly associated with other psychiatric disorders such as OCD, anxiety, eating disorders, and alcohol and substance abuse

All OCD-related disorders can be treated with CBT and SSRIs.

TRAUMA AND STRESSOR-RELATED DISORDERS

POST-TRAUMATIC STRESS DISORDER

Disorder characterized by clinically significant distress or impairment in daily functioning caused by exposure to an extreme, life-threatening traumatic event (eg, war, assault, injury, rape, accident, violent crime). Event can be either directly experienced or witnessed.

A

This person suffers from obsessive-compulsive personality disorder (OCPD). These patients are perfectionists, are preoccupied with rules and order, and are often inflexible. Unlike patients with obsessive-compulsive disorder, those with OCPD typically are not disturbed by their disease.

History/PE

- Patients experience severe psychological distress when exposed to stimuli that remind them of the event, resulting in avoidance of situations where exposure to triggers is possible

KEY FACT

Top causes of PTSD in male patients are (1) sexual assault and (2) war.
Top causes of PTSD in female patients are (1) childhood abuse and (2) sexual assault.

- High incidence of substance abuse, anxiety, and/or depression

Diagnosis

- Exposure to a traumatic event and the presence of one or more of the following:
    1. **Intrusive symptoms:** Re-experiencing the event through nightmares, flashbacks, or intrusive memories
    2. Avoidance of stimuli associated with the trauma
    3. Negative alterations in mood and cognition: Numbed responsiveness (eg, detachment, anhedonia), guilt, blaming of oneself
    4. Changes in arousal and reactivity: ↑ arousal (eg, hypervigilance, exaggerated startle response), sleep disturbances, aggression/irritability, and poor concentration
- Symptoms lead to significant distress or impairment in functioning
- Symptoms must persist for >1 month
- **Acute stress disorder:** Diagnosed if symptoms are present for ≤1 month
    - Clinical presentation is the same as PTSD
    - Symptoms last ≥3 days but <1 month
    - Symptoms present within 1 month of experiencing the traumatic event

Treatment

- **Best initial treatment:**
    - PTSD: CBT + SSRIs or SNRIs
    - Acute stress disorder: Trauma-focused CBT or eye movement desensitization and reprocessing therapy
- **Pharmacotherapy:** SSRIs or SNRIs as a second-line option
    - Prazosin (α_1-blocker) is used to treat PTSD-related nightmares

- CBT alone, SSRIs alone, or a combination of both have been found to be similarly effective

NEUROCOGNITIVE DISORDERS

Disorders that affect memory, orientation, judgment, and attention.

Dementia (Major Neurocognitive Disorder)

A decline in cognitive functioning with global deficits. Level of consciousness is stable (vs delirium). Prevalence is highest among those >85 years of age. The course is persistent and progressive. The most common causes are Alzheimer disease (65%) and vascular dementia (20%). Other causes are outlined in the mnemonic **DEMENTIASS**.

MNEMONIC

Causes of dementia—

DEMENTIASS

Degenerative diseases (Parkinson, Huntington, dementia with Lewy bodies [DLB])
Endocrine (thyroid, parathyroid, pituitary, adrenal)
Metabolic (alcohol, electrolytes, vitamin B_{12} deficiency, glucose, hepatic, renal, Wilson disease)
Exogenous (heavy metals, carbon monoxide, drugs)
Neoplasia
Trauma (subdural hematoma)
Infection (meningitis, encephalitis, endocarditis, syphilis, HIV, prion diseases, Lyme disease)
Affective disorders (pseudodementia)
Stroke/**S**tructure (vascular dementia, ischemia, vasculitis, normal-pressure hydrocephalus)

History/PE

- Patients with dementia are usually not concerned about their cognitive decline and are often accompanied to the doctor visit by a family member or friend (vs major depressive disorder [MDD]/pseudodementia).
- Dementia is characterized by progressive memory impairment that can be classified into the following four stages:
  - **Preclinical:** Slight forgetfulness, fully oriented, and capable of caring for oneself.
  - **Mild:** Moderate memory loss, impaired executive function, impaired function at home but capable of maintaining most chores. Personal hygiene may need prompting.
  - **Moderate:** Severe memory loss, inability to recognize friends (agnosia), impaired social judgement; requires assistance with dressing and personal hygiene.
  - **Severe:** Severe memory loss, oriented only to person, completely dependent on others for ADLs; may develop aphasia and become incommunicable.
- Personality, mood, and behavior changes are common (eg, wandering and aggression).

Diagnosis

- Diagnosis is clinical. History, PE, and Mini-Mental State Examination (MMSE) <24 or Montreal Cognitive Assessment (MoCA) <26
- The physician should **rule out treatable causes of dementia.** Obtain a urinalysis (UA), complete blood cell count (CBC), erythrocyte sedimentation rate (ESR), vitamin B_{12}, folate, comprehensive metabolic panel (CMP), thyroid function tests (TFTs), HIV, rapid plasma reagin (RPR), and a head CT/MRI.
- Definitive diagnosis requires autopsy and histopathologic exam (rarely performed).
- Table 2.13-8 outlines key characteristics distinguishing dementia from delirium.

TABLE 2.13-8. **Delirium vs Dementia**

CHARACTERISTIC	DELIRIUM	DEMENTIA
Level of attention	Impaired (fluctuating)	Usually alert
Onset	Acute	Gradual
Course	Fluctuating from hour to hour, "sundowning"	Progressive deterioration
Consciousness	Clouded	Intact
Hallucinations	Present (often visual or tactile)	Occur in ~30% of patients in highly advanced disease
EEG changes	Diffuse background slowing	None
Prognosis	Reversible	Largely irreversible, but up to 15% of cases are a result of treatable causes and are reversible
Treatment	Treat underlying causes Environmental changes (eg, ↓ stimuli, providing frequent orientation to day/time, keeping shades up during daytime to reestablish circadian rhythm) Low-dose antipsychotics for disruptive behaviors (agitation, combativeness)	Cholinesterase inhibitors; low-dose antipsychotics (primarily for behavior disturbances) Environmental changes

Treatment

- **Pharmacotherapy:**
  - **Best initial treatment:** Cholinesterase inhibitors (donepezil, rivastigmine, galantamine)
  - **Moderate/severe Alzheimer dementia:** Addition of memantine (N-methyl-D-aspartate [NMDA] antagonist)
  - **Aggression/psychosis:** Low-dose antipsychotics (use with caution in older adults; black box warning for increased mortality)
  - Avoidance of benzodiazepines, which may exacerbate disinhibition and confusion
- Provide environmental cues and a rigid structure for the patient's daily life
- Family, caregiver, and patient education and support are imperative

DELIRIUM

An acute disturbance of consciousness with altered cognition that develops over a short period (usually hours to days). Children, older adults, and hospitalized patients (eg, intensive care unit [ICU] psychosis) are particularly susceptible. Symptoms are potentially reversible if the underlying cause can be treated.

History/PE

- Delirium presents with acute onset of waxing and waning consciousness with lucid intervals and perceptual disturbances (hallucinations, illusions, delusions).
- Patients may be combative, anxious, paranoid, or stuporous.
- Patients have ↓ attention span and short-term memory, a reversed sleep-wake cycle, and ↑ symptoms at night (sundowning).
- Procure history and conduct physical and neurologic examinations.
- Check vital signs, pulse oximetry, electrolytes, glucose, CBC, and UA.

Diagnosis

- **Best initial test:** Investigate common causes of delirium.
- A urinary tract infection (UTI) is a common cause of delirium in older adults.
- Note recent medication additions/changes (eg, narcotics, anticholinergics, steroids, benzodiazepines).
- Evaluate for substance abuse and medical problems (eg, renal failure, liver failure).

KEY FACT

Confusion Assessment Method (CAM): Evidence-based tool used by medical personnel to help diagnose delirium. Diagnosis can be made if both 1 and 2 are present + *either* 3 or 4:

1. Acute onset or fluctuating course
2. Inattention
3. Disorganized thinking
4. Altered level of consciousness

Questions on the CAM are designed to confirm whether these features are present or absent.

MNEMONIC

Major causes of delirium—

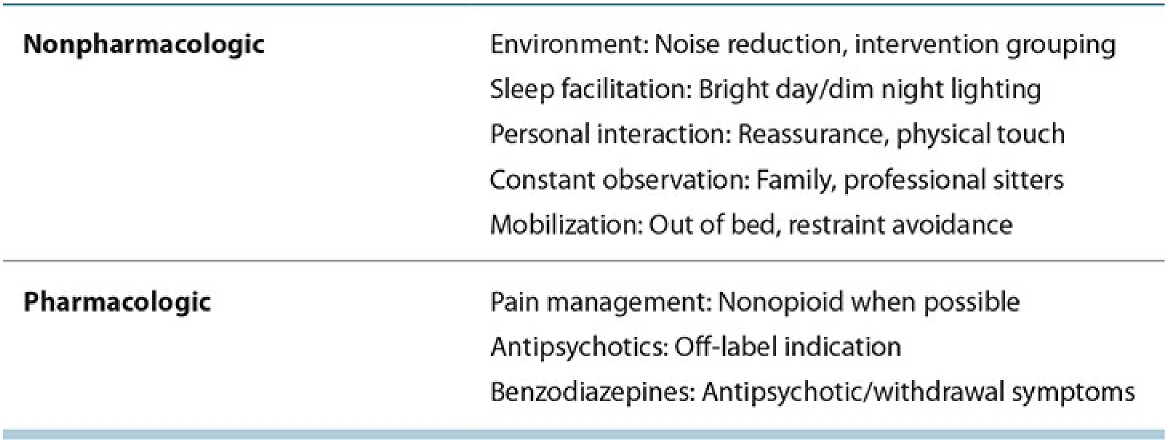
I WATCH DEATH

Infection
Withdrawal
Acute metabolic/substance **A**buse
Trauma
CNS pathology
Hypoxia
Deficiencies
Endocrine
Acute vascular/MI
Toxins/drugs
Heavy metals

Treatment

- A combination of pharmacologic and nonpharmacologic interventions is often necessary (see Table 2.13-9).

TABLE 2.13-9. **Management of Delirium Symptoms**



Nonpharmacologic	Environment: Noise reduction, intervention grouping Sleep facilitation: Bright day/dim night lighting Personal interaction: Reassurance, physical touch Constant observation: Family, professional sitters Mobilization: Out of bed, restraint avoidance
Pharmacologic	Pain management: Nonopioid when possible Antipsychotics: Off-label indication Benzodiazepines: Antipsychotic/withdrawal symptoms

- Treat underlying causes (delirium is often reversible).
- Normalize fluids and electrolytes.
- Optimize the sensory environment and provide necessary visual and hearing aids.
- Use low-dose antipsychotics (eg, haloperidol) for agitation and psychotic symptoms.
- Conservative use of physical restraints may be necessary to prevent harm to the patient or others.

KEY FACT

It is common for delirium to be superimposed on dementia.

MOOD DISORDERS

Also known as affective disorders.

MAJOR DEPRESSIVE DISORDER

A mood disorder characterized by one or more major depressive episodes (MDEs). The male-to-female ratio is 1:2; lifetime prevalence ranges from 15% to 25%. Onset is usually in the mid-20s; in older adults, prevalence ↑ with age. Chronic illness and stress ↑ risk. Approximately 2% to 9% of patients die by suicide.

MNEMONIC

Symptoms of a depressive episode—

SIG E CAPS

Sleep (hypersomnia or insomnia)
Interest (loss of interest or pleasure in activities)
Guilt (feelings of worthlessness or inappropriate guilt)
Energy (↓) or fatigue

Concentration (↓)
Appetite (↑ or ↓) or weight (↑ or ↓)
Psychomotor agitation or retardation
Suicidal ideation

KEY FACT

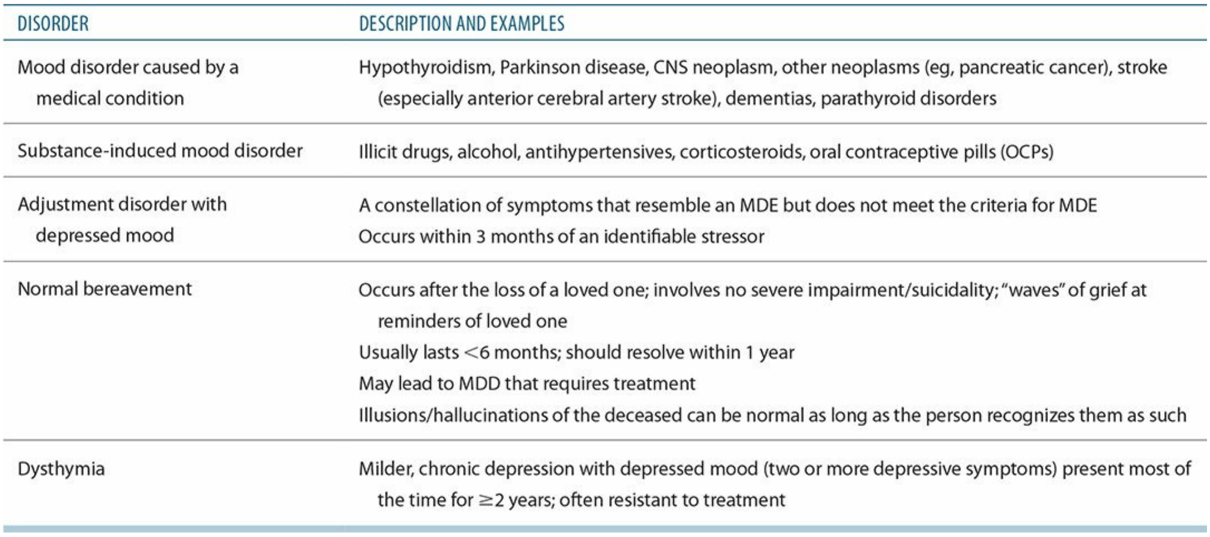
Major depressive episodes can be present in major depressive disorder or in bipolar disorder types I and II.

KEY FACT

Minors with suicidal ideation should be hospitalized involuntarily with or without parental consent (although parental consent is preferred).

Table 2.13-10 outlines differential diagnosis of conditions that can be mistaken for depression.

TABLE 2.13-10. **Differential Diagnosis of Major Depressive Disorder**



DISORDER	DESCRIPTION AND EXAMPLES
Mood disorder caused by a medical condition	Hypothyroidism, Parkinson disease, CNS neoplasm, other neoplasms (eg, pancreatic cancer), stroke (especially anterior cerebral artery stroke), dementias, parathyroid disorders
Substance-induced mood disorder	Illicit drugs, alcohol, antihypertensives, corticosteroids, oral contraceptive pills (OCPs)
Adjustment disorder with depressed mood	A constellation of symptoms that resemble an MDE but does not meet the criteria for MDE Occurs within 3 months of an identifiable stressor
Normal bereavement	Occurs after the loss of a loved one; involves no severe impairment/suicidality; "waves" of grief at reminders of loved one Usually lasts <6 months; should resolve within 1 year May lead to MDD that requires treatment Illusions/hallucinations of the deceased can be normal as long as the person recognizes them as such
Dysthymia	Milder, chronic depression with depressed mood (two or more depressive symptoms) present most of the time for ≥2 years; often resistant to treatment

Subtypes include the following:

- **Psychotic features:** Generally mood-congruent delusions/hallucinations. Psychosis only occurs during the MDD episode (distinguished from schizoaffective disorder).
- **Postpartum:** Occurs within 1 to 3 months postpartum; has a 10% incidence and a high risk for recurrence. Psychotic symptoms are common (see Table 2.13-11).

TABLE 2.13-11. **Differential Diagnosis of Postpartum Disorders**

SUBTYPE	TIME OF ONSET	SYMPTOMS
Postpartum "blues"	Within 2 weeks of delivery	Sadness, moodiness, emotional lability No thoughts about hurting self or baby
Postpartum depression	1–3 months postdelivery	Same as earlier plus sleep disturbances and anxiety May have thoughts about hurting self and/or baby
Postpartum psychosis	2–3 weeks postdelivery	Delusions, disorganized behavior May have thoughts about hurting baby

- **Atypical:** Characterized by weight gain, hypersomnia, and rejection sensitivity.
- **Seasonal:** Depressive episodes occurring during a specific season (most commonly winter). This subtype responds well to light therapy with or without antidepressants.

MNEMONIC

TCA toxicity—

Tri Cs

Convulsions
Coma
Cardiac arrhythmias

Diagnosis

Diagnosis requires depressed mood or anhedonia (loss of interest/pleasure) and five or more signs/symptoms from the SIG E CAPS mnemonic for ≥2 weeks.

Treatment

- **Pharmacotherapy: Best initial treatment** is with an SSRI (eg, fluoxetine [drug of choice], sertraline, paroxetine, citalopram, escitalopram). A partial response to SSRIs can be augmented with bupropion or aripiprazole.
  - Allow 2 to 6 weeks for medication to take effect. Dose can be adjusted as needed.
  - The patient should continue taking the medication for at least 6 months (at the same effective dose) beyond the time of achieving full remission.
  - If a patient fails to respond to the initial antidepressant, they can be switched to another first-line agent (SSRI). Agents alternatively used, based on patient comorbidities and second-line treatment, include those listed in Table 2.13-12.

TABLE 2.13-12. **Indications and Side Effects of Common Antidepressants**

DRUG CLASS	EXAMPLES	INDICATIONS	ADVERSE EFFECTS
SSRIs	Fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine	Depression, anxiety	Sexual side effects, GI distress, agitation, insomnia, tremor, diarrhea Serotonin syndrome (fever, myoclonus, hyperreflexia, altered mental status, cardiovascular collapse) can occur if SSRIs are used with MAO inhibitors, illicit drugs, or herbal medications Paroxetine should be avoided during pregnancy; it can cause cardiac defects (first trimester) and pulmonary HTN (third trimester) in the fetus Discontinuation syndrome (flulike symptoms, nausea, insomnia, sensory disturbances) occurs with abrupt cessation of shorter-acting agents
Atypical antidepressants	Bupropion, mirtazapine, trazodone	Depression, anxiety Smoking cessation (bupropion)	Bupropion: ↓ seizure threshold; minimal sexual side effects Contraindicated in patients with eating disorders and seizure disorders Mirtazapine: Weight gain, sedation, minimal sexual side effects Trazodone: Highly sedating; priapism
SNRIs	Venlafaxine, duloxetine	Depression, anxiety, neuropathic pain	Noradrenergic side effects at higher doses Venlafaxine: Diastolic HTN
TCAs	Nortriptyline, desipramine, amitriptyline, imipramine, clomipramine	Depression, anxiety, neuropathic pain, migraine headaches, enuresis (imipramine), OCD (clomipramine)	Antihistaminic effects: Sedation, weight gain Anticholinergic effects: Dry mouth, tachycardia, urinary retention Antiadrenergic effects: Orthostatic hypotension TCA overdose can be lethal and cause convulsions (seizures), coma, cardiotoxicity (prolonged conduction through AV node, prolonged QRS), hyperpyrexia, and respiratory depression Treatment for TCA overdose: Sodium bicarbonate if prolonged QRS (>100 msec), hypotensive, or ventricular arrhythmia; sodium bicarbonate alleviates depressant effect of TCA on cardiac fast Na^+ channels
MAO inhibitors	Phenelzine, tranylcypromine, selegiline (also available in patch form)	Depression, especially atypical	Hypertensive crisis if taken with foods high in tyramine (eg, aged cheese, red wine) Sexual side effects, orthostatic hypotension, weight gain

AV, Atrioventricular; *HTN,* hypertension; *MAO,* monoamine oxidase.

- **Most effective treatment:** Psychotherapy + antidepressants are more effective than either treatment alone.
- **ECT:** A small electrical current is used to induce a generalized seizure under anesthesia. It is a safe and highly effective treatment option for severe depression. ECT usually requires two to three treatments per week for a total of 6 to 12 treatments. **Indications are as follows:**
  - Refractory or treatment-resistant depression
  - MDD with psychotic features
  - Need for rapid improvement: Actively suicidal, refusal to eat/drink, catatonia, pregnancy
  - Bipolar depression or mania
  - No absolute contraindications. Relative contraindications include recent myocardial infarction (MI)/stroke, intracranial mass, and high anesthetic risk
  - **Adverse effects:** Anterograde amnesia, postictal confusion, arrhythmias, and headache
- **Phototherapy:** This is effective for depression with seasonal pattern.

KEY FACT

It is important to rule out bipolar disorder before treating major depressive disorder because SSRIs can cause mania in those with bipolar disorder.

KEY FACT

Those with two or more episodes should be prescribed maintenance antidepressant therapy for 1 to 3 years. Those with three or more episodes should have indefinite therapy prescribed.

KEY FACT

Discontinue SSRIs at least 2 weeks before starting an MAOI. Wait 5 weeks if the patient was on fluoxetine due to its long half-life.

Q

A 23-year-old woman complains of difficulty falling asleep and worsening anxiety that began 2 months earlier after she was involved in a minor biking accident (bike vs car) in which she did not suffer any injuries. Since the accident, she has refused to participate in any outdoor activities. What is her most likely diagnosis?

PERSISTENT DEPRESSIVE DISORDER (DYSTHYMIA)

History/PE

- Persistent depressive disorder refers to a chronic depressed mood including at least two depressive symptoms (one in children) present on most days for >2 years with no symptom-free periods lasting more than 2 months.
- Patients often have felt depressed for as long as they can remember.
- **Double depression:** Diagnosed if patient meets criteria for MDD during dysthymic periods.

A

Adjustment disorder, which consists of emotional and behavioral symptoms that develop in response to an identifiable stressor, lasts >1 month and <6 months, and does not have five or more symptoms of major depressive disorder.

Treatment

- Psychotherapy is the most effective treatment.
- Persistent depressive disorder is often resistant to treatment. Treatments to consider are antidepressants (eg, SSRIs) and ECT.

ADJUSTMENT DISORDER

Clinically significant distress following a profound life change (eg, divorce, unemployment, financial issues**,** romantic breakup); it is not severe enough to meet criteria for another mental disorder.

History/PE

- Patients develop anxiety or depressive symptoms (eg, anhedonia, depressed mood, weight loss) following a stressful life event (eg, divorce, death of family member, change in school/work).
    - Event is not life-threatening.
    - Symptoms present within 3 months after onset of the stressor. Adjustment disorder resolves within 6 months after event is over.
    - Adjustment disorder causes social or occupational dysfunction, as opposed to a normal stress reaction.

Treatment

- **Best initial treatment:** Psychotherapy focusing on coping skills and supportive counseling
- No pharmacologic treatment

KEY FACT

Premenstrual dysphoric disorder (PMDD) presents the same as dysthymia, but the symptoms in PMDD are cyclic, whereas dysthymia is present all the time.

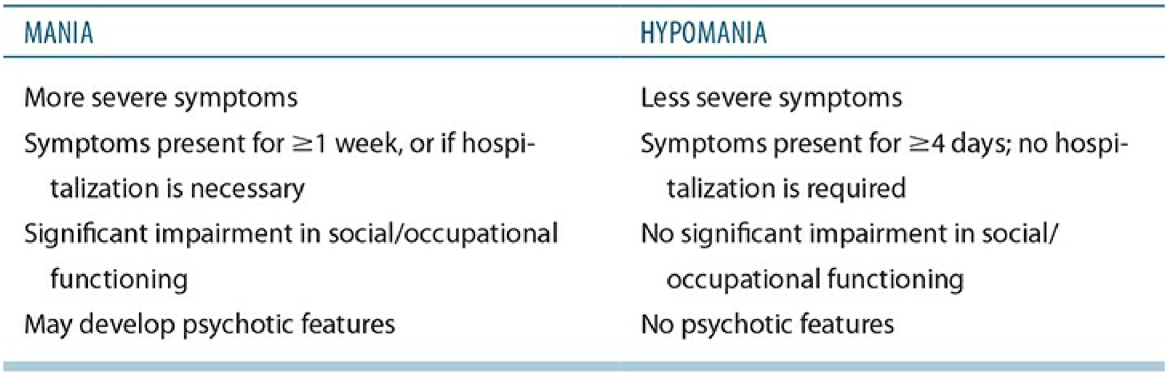
BIPOLAR AND RELATED DISORDERS

Psychiatric illnesses characterized by episodes of mania or hypomania ± MDE. A family history significantly ↑ risk. The average age of onset is 20 years, and the frequency of mood episodes tends to ↑ with age. Up to 10% to 15% of those affected complete suicide. Bipolar and related disorders are classified into the following subtypes: bipolar I, bipolar II, or cyclothymic disorder.

History/PE

- The mnemonic **DIG FAST** outlines the clinical presentation of mania. See Table 2.13-13 to differentiate mania from hypomania. May report excessive engagement in pleasurable activities (eg, excessive spending or sexual activity), reckless behaviors, and/or psychotic features.

TABLE 2.13-13. Mania vs Hypomania



MANIA	HYPOMANIA
More severe symptoms	Less severe symptoms
Symptoms present for ≥1 week, or if hospitalization is necessary	Symptoms present for ≥4 days; no hospitalization is required
Significant impairment in social/occupational functioning	No significant impairment in social/occupational functioning
May develop psychotic features	No psychotic features

MNEMONIC

Symptoms of mania—

DIG FAST

Distractibility
Insomnia (↓ need for sleep)
Grandiosity (↑ self-esteem)/**G**oal directed
Flight of ideas (or racing thoughts)
Activities/psychomotor **A**gitation
Sexual indiscretions/other pleasurable activities
Talkativeness/pressured speech

- Patients may or may not have history of a major depressive episode (see **SIG E CAPS** mnemonic).
- Antidepressants may trigger manic episodes (without a mood stabilizer). Ropinirole and other dopamine agonists can also cause manialike symptoms.

Diagnosis

Figure 2.13-1 outlines different psychiatric disorders and the duration of symptoms as part of their respective diagnostic criteria in the *DSM-5*.

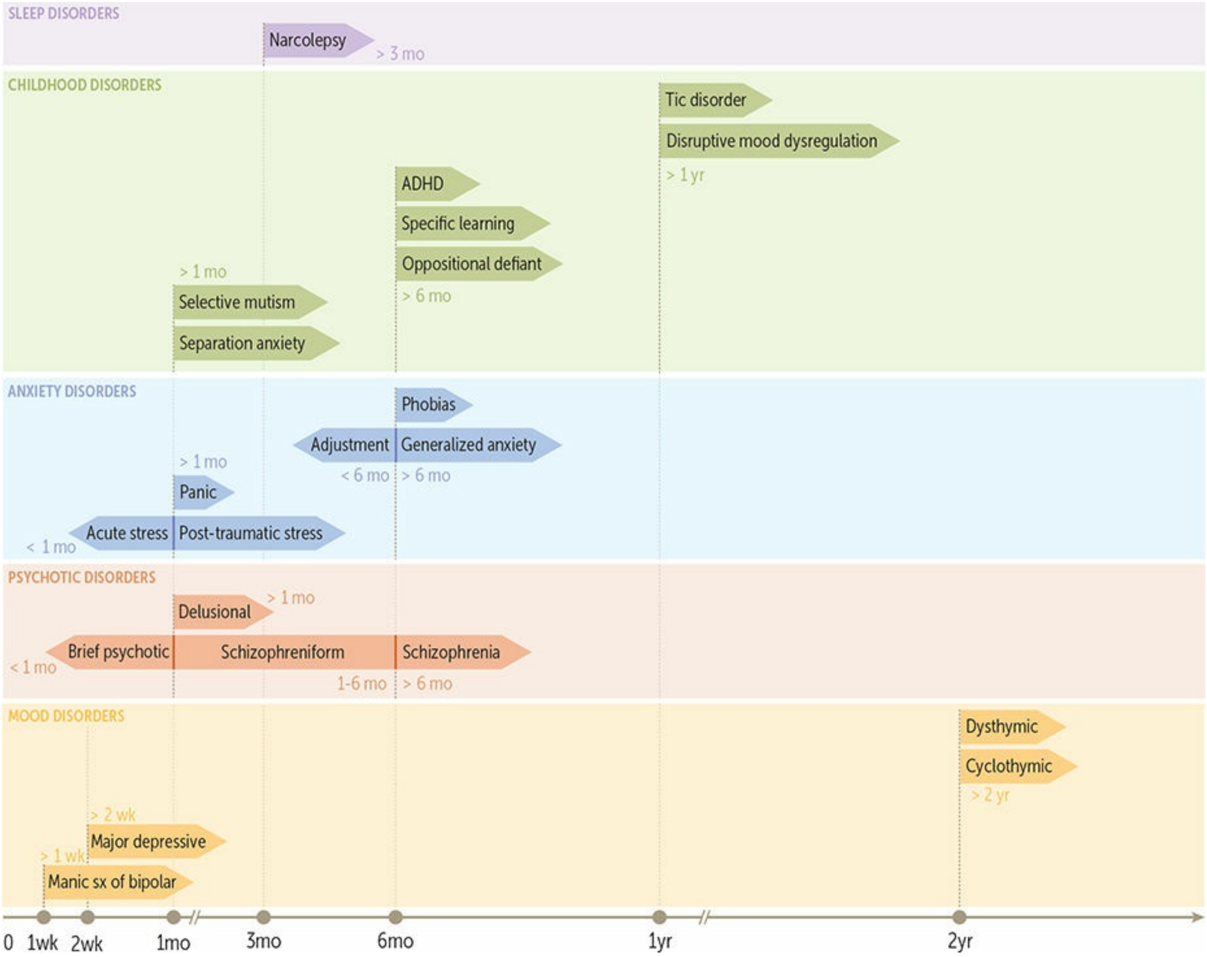

SLEEP DISORDERS
Narcolepsy
> 3 mo
CHILDHOOD DISORDERS
Tic disorder
Disruptive mood dysregulation
> 1 yr
ADHD
Specific learning
Oppositional defiant
> 6 mo
> 1 mo
Selective mutism
Separation anxiety
ANXIETY DISORDERS
Phobias
Adjustment
Generalized anxiety
< 6 mo
> 6 mo
> 1 mo
Panic
Acute stress
Post-traumatic stress
< 1 mo
PSYCHOTIC DISORDERS
Delusional
> 1 mo
Brief psychotic
Schizophreniform
Schizophrenia
< 1 mo
1-6 mo
> 6 mo
MOOD DISORDERS
Dysthymic
Cyclothymic
> 2 yr
> 2 wk
Major depressive
> 1 wk
Manic sx of bipolar
0
1wk
2wk
1mo
3mo
6mo
1yr
2yr

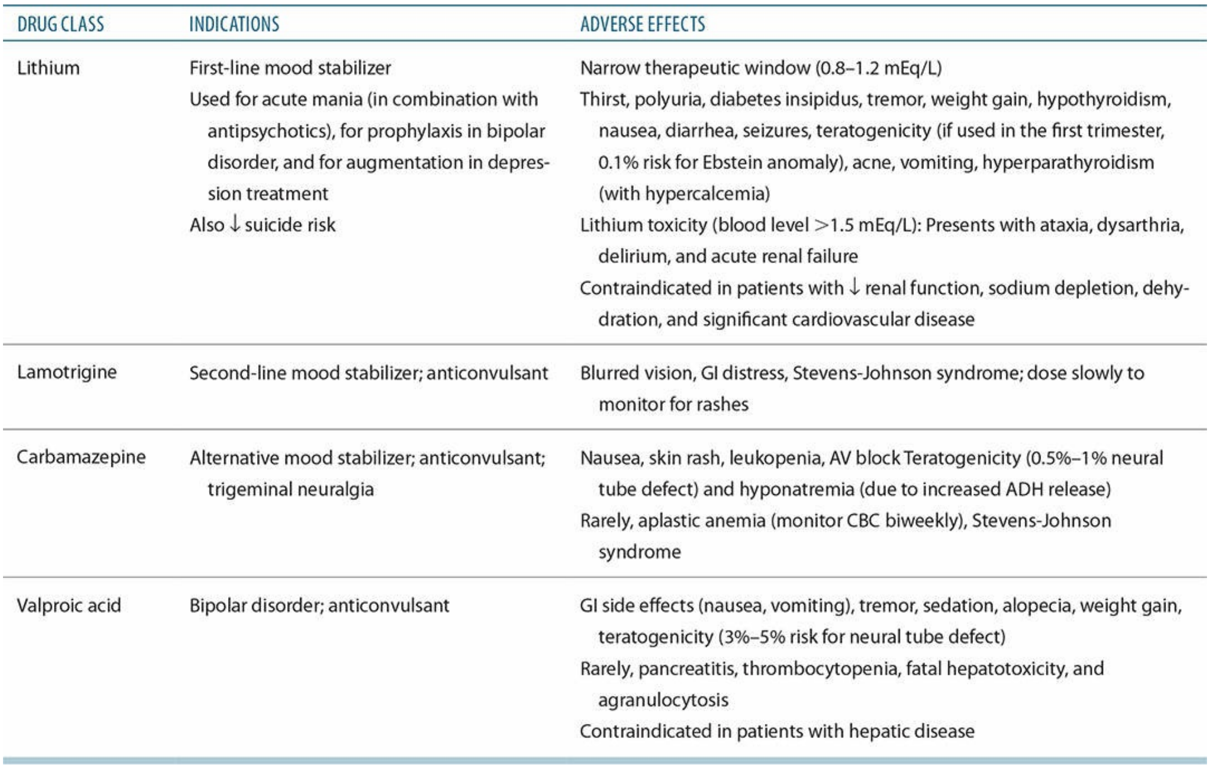
FIGURE 2.13-1. **Diagnostic criteria by symptom duration.** Psychiatric conditions have overlapping symptoms and presentations; therefore, emphasis is placed on symptom duration as part of the diagnostic criteria of most conditions in the *DSM-5*. (Adapted with permission from USMLE-Rx.com.)

- Symptoms must not be caused by substance abuse or a medical condition.
- **Bipolar I:**
  - Manic episode
  - Major depressive episode not required for diagnosis
- **Bipolar II:**
  - Hypomanic episode
  - One or more MDEs
- **Cyclothymic disorder:** Alternating periods of the following symptoms for at least 2 years:
  - Hypomanic symptoms that do not meet criteria for hypomania
  - Depressive symptoms that do not meet criteria for MDE

Treatment

- **Bipolar I and bipolar II:**
  - **Maintenance therapy:** Mood stabilizers (see Table 2.13-14). Most patients require lifelong mood stabilizer treatment.

TABLE 2.13-14. **Mood Stabilizers**



DRUG CLASS	INDICATIONS	ADVERSE EFFECTS
Lithium	First-line mood stabilizer Used for acute mania (in combination with antipsychotics), for prophylaxis in bipolar disorder, and for augmentation in depression treatment Also ↓ suicide risk	Narrow therapeutic window (0.8–1.2 mEq/L) Thirst, polyuria, diabetes insipidus, tremor, weight gain, hypothyroidism, nausea, diarrhea, seizures, teratogenicity (if used in the first trimester, 0.1% risk for Ebstein anomaly), acne, vomiting, hyperparathyroidism (with hypercalcemia) Lithium toxicity (blood level >1.5 mEq/L): Presents with ataxia, dysarthria, delirium, and acute renal failure Contraindicated in patients with ↓ renal function, sodium depletion, dehydration, and significant cardiovascular disease
Lamotrigine	Second-line mood stabilizer; anticonvulsant	Blurred vision, GI distress, Stevens-Johnson syndrome; dose slowly to monitor for rashes
Carbamazepine	Alternative mood stabilizer; anticonvulsant; trigeminal neuralgia	Nausea, skin rash, leukopenia, AV block Teratogenicity (0.5%–1% neural tube defect) and hyponatremia (due to increased ADH release) Rarely, aplastic anemia (monitor CBC biweekly), Stevens-Johnson syndrome
Valproic acid	Bipolar disorder; anticonvulsant	GI side effects (nausea, vomiting), tremor, sedation, alopecia, weight gain, teratogenicity (3%–5% risk for neural tube defect) Rarely, pancreatitis, thrombocytopenia, fatal hepatotoxicity, and agranulocytosis Contraindicated in patients with hepatic disease

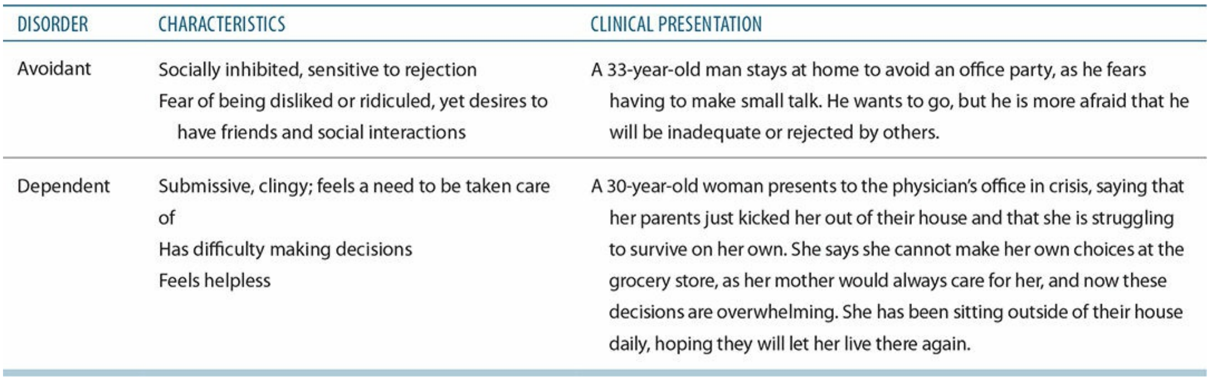
  - **Best initial treatment:** Lithium
- **Acute mania:** Considered a psychiatric emergency because of impaired judgment and risk for harm to self or others
- **Mild to moderate mania:** Atypical antipsychotics (olanzapine, quetiapine)
- Severe mania: Mood stabilizer (lithium/valproate) + antipsychotic
- Refractory mania: ECT
- Mania/hypomania in pregnancy: Antipsychotics—typical antipsychotics (eg, haloperidol) are generally first line and have fewer risks to the developing fetus than mood stabilizers. ECT can be used for severe or refractory mania in pregnancy
- **Bipolar depression:** Mood stabilizers with or without antidepressants. The patient should begin taking the mood stabilizer first to avoid inducing mania. The physician may also try a combination of mood stabilizer and antipsychotic if monotherapy fails

PERSONALITY DISORDERS

Personality can be defined as an individual’s set of emotional and behavioral traits, which are generally stable and predictable. Personality disorders are defined when one’s traits become chronically rigid and maladaptive, leading to social or occupational dysfunction. Disorders are outlined in Table 2.13-15.

TABLE 2.13-15. Signs and Symptoms of Personality Disorders

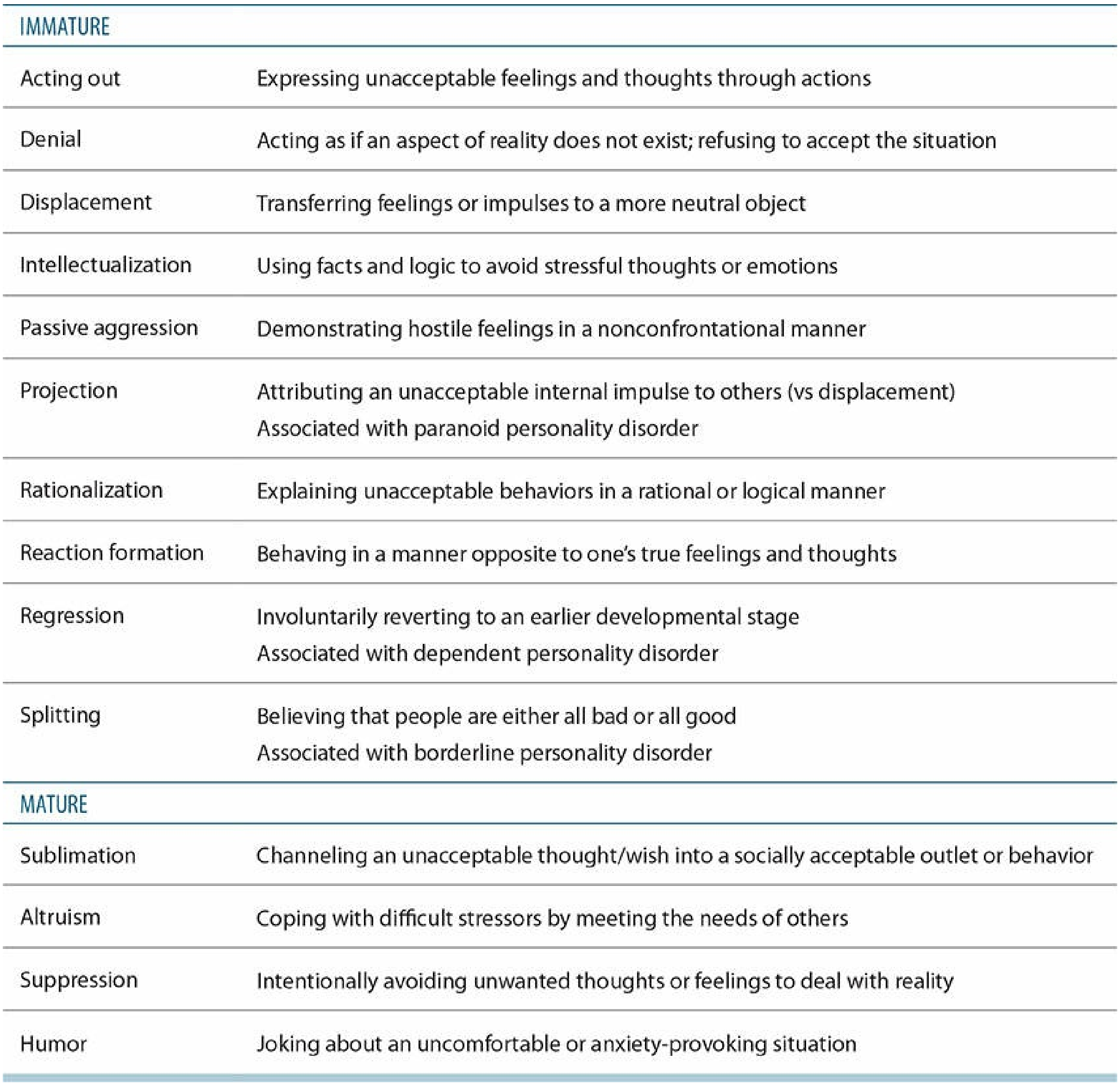
DISORDER	CHARACTERISTICS	CLINICAL PRESENTATION
CLUSTER A: "WEIRD"		
Paranoid	Distrustful, suspicious; interprets others' motives as malevolent Note: These patients commonly use projection as a defense mechanism	A 59-year-old man who lives alone constantly feels that his neighbor's children are spying on him and plotting to break into his home. He has installed security cameras all around his property to obtain proof. He feels he cannot trust the police to do a good job because they will probably take the side of his neighbors.
Schizoid	Isolated, detached "loners" who prefer to be alone Restricted emotional expression	A 66-year-old man who moves to Thailand alone after retirement, has no desire to remain in contact with his family, and is very distant in his interactions. He stays in his remote accommodations without unnecessary travel and does not crave interaction with the locals.
Schizotypal	Odd behavior, perceptions, and appearance Magical thinking; ideas of reference	A 35-year-old man with very strange ideas regarding the importance of crystals and their effects on health. He meticulously mines and collects crystals, feeling that they will one day prevent him from acquiring cancer.
CLUSTER B: "WILD"		
Borderline	Unstable mood, relationships, and self-image; feelings of emptiness Impulsive History of suicidal ideation or self-harm Note: These patients often employ splitting as a defense mechanism (see Table 2.13-16)	A 28-year-old woman presents to the clinic after having praised her new clinician as better than all the others. She reveals that she fired her last therapist, as he was not really helping. The physician notices she has fresh cuts in a row on her forearm.
Histrionic	Excessively emotional and attention seeking Sexually provocative; theatrical	A 35-year-old woman presents to clinic wearing a very low-cut blouse and adjusting her position to draw attention to herself. When she does not get attention, she breaks into tears, saying that no one notices her, not even her friends.
Narcissistic	Grandiose; needs admiration; has sense of entitlement Lack of empathy	A 45-year-old man impatiently taps his foot in the waiting room of the office. He approaches the receptionist, demands to know where the doctor is, and tells her that he will have her fired and the doctor reported if he is not seen shortly as he believes his time is being wasted in a queue.
Antisocial	Violates rights of others, social norms, and laws; impulsive; lacks remorse Must be >18 years of age Evidence of conduct disorder before 15 years of age	A 22-year-old man who has committed a brutal assault is at a court-ordered psychiatry appointment. When a teenager, he was in juvenile detention for theft. He says he does not need to be seen by a "shrink," and that because he was offended by the victim, they deserved to be assaulted.
CLUSTER C: "WORRIED AND WIMPY"		
Obsessive-compulsive	Preoccupied with perfection, order, and control at the expense of efficiency Inflexible morals and values Note: Remember, in contrast to obsessive-compulsive disorder, patients with obsessive-compulsive **personality** disorder do not feel their behavior is problematic (ego-syntonic); they also do not have true obsessions and compulsions	A 35-year-old woman presents to the office at the request of her boss, who feels she is too focused on minute details on team projects and does not allow others to participate for fear of unwanted errors. She does not see anything wrong with this style of work, as she believes her coworkers cannot be trusted to pay adequate attention to detail.



DISORDER	CHARACTERISTICS	CLINICAL PRESENTATION
Avoidant	Socially inhibited, sensitive to rejection Fear of being disliked or ridiculed, yet desires to have friends and social interactions	A 33-year-old man stays at home to avoid an office party, as he fears having to make small talk. He wants to go, but he is more afraid that he will be inadequate or rejected by others.
Dependent	Submissive, clingy; feels a need to be taken care of Has difficulty making decisions Feels helpless	A 30-year-old woman presents to the physician's office in crisis, saying that her parents just kicked her out of their house and that she is struggling to survive on her own. She says she cannot make her own choices at the grocery store, as her mother would always care for her, and now these decisions are overwhelming. She has been sitting outside of their house daily, hoping they will let her live there again.

Defense mechanisms are methods of dealing with anxiety or conflicts of the ego (eg, anger, guilt, inadequacy, grief). These can be immature (more primitive) or mature (more sophisticated). Immature defense mechanisms are **common in personality disorders.** Important defense mechanisms are outlined in Table 2.13-16.

TABLE 2.13-16. Defense Mechanisms



IMMATURE	
Acting out	Expressing unacceptable feelings and thoughts through actions
Denial	Acting as if an aspect of reality does not exist; refusing to accept the situation
Displacement	Transferring feelings or impulses to a more neutral object
Intellectualization	Using facts and logic to avoid stressful thoughts or emotions
Passive aggression	Demonstrating hostile feelings in a nonconfrontational manner
Projection	Attributing an unacceptable internal impulse to others (vs displacement) Associated with paranoid personality disorder
Rationalization	Explaining unacceptable behaviors in a rational or logical manner
Reaction formation	Behaving in a manner opposite to one's true feelings and thoughts
Regression	Involuntarily reverting to an earlier developmental stage Associated with dependent personality disorder
Splitting	Believing that people are either all bad or all good Associated with borderline personality disorder
MATURE	
Sublimation	Channeling an unacceptable thought/wish into a socially acceptable outlet or behavior
Altruism	Coping with difficult stressors by meeting the needs of others
Suppression	Intentionally avoiding unwanted thoughts or feelings to deal with reality
Humor	Joking about an uncomfortable or anxiety-provoking situation

Diagnosis

Diagnosis is clinical, and detailed history taking is imperative. Collateral information may be helpful. Patients typically deny or do not realize they have a problem (ego syntonic).

Treatment

- **Best initial treatment:** Psychotherapy
- Pharmacotherapy is reserved for cases with comorbid mood, anxiety, or psychotic signs/symptoms

MNEMONIC

Characteristics of personality disorders—

MEDIC

Maladaptive
Enduring
Deviate from cultural norms
Inflexible
Cause impairment in social or occupational functioning

SUBSTANCE USE DISORDERS

Substance use disorder is a maladaptive pattern of substance use that leads to clinically significant impairment. It can be applied to most substances of abuse. The patient must meet ≥2 of the 11 criteria within a 1-year period for diagnosis. The criteria can be grouped into four categories of symptoms and are as follows:

- **Impaired control:**
  1. Consumption of greater amounts of the substance than intended
  2. Failed attempts to cut down use or abstain from the substance
  3. Increased amount of time spent acquiring the substance, using it, or recovering from effects
  4. Craving
- **Social impairment:**
  5. Failure to fulfill responsibilities at work, school, or home
  6. Continued substance use despite recurrent social or interpersonal problems secondary to the effects of such use (eg, frequent arguments with spouse over the substance use)
  7. Isolation from life activities
- **Risky use:**
  8. Use of substances in physically hazardous situations (eg, driving while intoxicated)
  9. Continued substance abuse despite recurrent physical or psychological problems secondary to the effects of the substance use
- **Pharmacologic:**
  10. Tolerance and use of progressively larger amounts to obtain the same desired effects
  11. Withdrawal symptoms when not taking the substance

Tolerance and withdrawal are not needed to make the diagnosis.

- **Withdrawal:**
  - Physiologic syndrome that occurs when concentrations of a substance decline in an individual who has had prolonged heavy use of that substance
  - Symptoms vary greatly across substances, but when they occur, the individual is likely to consume the substance again in order to relieve the symptoms
  - For most substances, a history of withdrawal is usually associated with a more severe clinical course

Diagnosis/Treatment

- Diagnosis is typically clinical, and detailed history-taking is imperative
- **Lab tests:** Urine and blood toxicology screens, liver function tests (LFTs), and serum ethanol (EtOH)

KEY FACT

Pinpoint pupils are not always a reliable sign of opioid ingestion, because co-ingestions can lead to normal or enlarged pupils. Also look for a ↓ respiratory rate, track marks, and ↓ breath sounds.

KEY FACT

Acute pain management is the same for all patients with severe pain refractory to NSAIDs regardless of a history of substance abuse. In the appropriate clinical setting, prior substance abuse is not a contraindication to the use of opioids in pain management and requires a nonjudgmental environment and shared decision making.

- Severity is determined by number of symptoms present
  - Mild: Two to three; moderate: four to five; severe: six or more
  - Symptoms of intoxication and withdrawal from selected drugs are described in Table 2.13-17.

TABLE 2.13-17. **Signs and Symptoms of Substance Abuse**

DRUG	INTOXICATION	WITHDRAWAL
DEPRESSANTS		
Alcohol	Disinhibition, emotional lability, slurred speech, ataxia, aggression, blackouts, hallucinations, memory impairment, impaired judgment, stupor, coma	6–24 hours: Anxiety, tremor, tachycardia, HTN 12–24 hours: Hallucinations 12–48 hours: Seizures 48–96 hours: DTs, fever, agitation, HTN, hallucinations
Opioids	Euphoria leading to apathy, CNS depression, constipation, pupillary constriction, respiratory depression (life-threatening in overdose), bradycardia Acute reversal of opioid intoxication: Naloxone (short acting so repeat dosing needed) To prevent relapse: Naltrexone (longer acting)	Dysphoria, insomnia, anorexia, myalgias, fever, lacrimation, diaphoresis, dilated pupils, rhinorrhea, piloerection, tachycardia, nausea, vomiting, stomach cramps, diarrhea, yawning Opioid withdrawal is not life-threatening, "hurts all over," and does not cause seizures; it can be treated with buprenorphine or methadone
Synthetic opioids	Contains MPTP (synthetic heroin) leading to Parkinson-like disorder and loss of pigmented neurons in the substantia nigra	None
Barbiturates	Low safety margin; respiratory depression	Anxiety, seizures, delirium, life-threatening cardiovascular collapse
Benzodiazepines	Interactions with alcohol, amnesia, ataxia, somnolence, mild respiratory depression Should not be used for insomnia in older adults; can cause paradoxical agitation even in relatively low doses	Rebound anxiety, seizures, tremor, insomnia, HTN, tachycardia, death
Inhalants (solvents, glue, fuels)	Tachycardia; nystagmus; tremor; ataxia; slurred speech; unconsciousness followed by drowsiness and headache; perioral rash, common among adolescents Short duration of action Long-term use can lead to irreversible CNS damage and polyneuropathy (due to vitamin B_{12} deficiency)	Dysphoria, headache, irritability
STIMULANTS		
Amphetamines	Psychomotor agitation, impaired judgment, HTN, pupillary dilation, tachycardia, fever, diaphoresis, anxiety, angina, euphoria, grandiosity, prolonged wakefulness/attention, arrhythmias, delusions, seizures, hallucinations, skin excoriations, poor dentition ("meth mouth") Haloperidol can be given for severe agitation and symptom-targeted medications (eg, antiemetics, NSAIDs)	Postuse "crash" with anxiety, lethargy, headache, stomach cramps, ↑ appetite, fatigue, depression/dysphoria, sleep disturbance, nightmares

DRUG	INTOXICATION	WITHDRAWAL
Cocaine	Psychomotor agitation, euphoria, impaired judgment, tachycardia, pupillary dilation, HTN, paranoia, hallucinations, "cocaine bugs" (the feeling of bugs crawling under one's skin), sudden death Chronic use causes ↓ appetite, weight loss, erythema of the nasal turbinates and septum perforation ECG changes from ischemia are often seen ("cocaine chest pain") Tx: Benzodiazepines, nonselective α-/β-blockers (eg, labetalol)	Postuse "crash" with hypersomnolence, depression, malaise, ↑ appetite, angina, suicidality, nightmares
Caffeine	Restlessness, insomnia, diuresis, muscle twitching, arrhythmias, tachycardia, flushed face, psychomotor agitation	Headache, lethargy, depression, weight gain, irritability, craving
Nicotine	Restlessness, insomnia, anxiety, arrhythmias	Irritability, headache, anxiety, weight gain, craving, bradycardia, difficulty concentrating, insomnia
HALLUCINOGENS		
Phencyclidine hydrochloride (PCP)	Assaultive/combative, belligerence, psychosis, violence, impulsiveness, psychomotor agitation, fever, tachycardia, vertical/horizontal nystagmus, HTN, impaired judgment, ataxia, seizures, delirium Benzodiazepines or haloperidol can treat severe symptoms; otherwise, physician should offer reassurance Gastric lavage can help eliminate the drug	Recurrence of intoxication symptoms caused by reabsorption in the GI tract; sudden onset of severe, random violence
Lysergic acid diethylamide (LSD)	Marked anxiety or depression, delusions, visual hallucinations, flashbacks, pupillary dilation, impaired judgment, diaphoresis, tachycardia, HTN, heightened senses (eg, colors become more intense) Tx: supportive counseling, traditional antipsychotics for psychotic symptoms, benzodiazepines for anxiety	None
Marijuana (tetrahydrocannabinol [THC], cannabis)	Euphoria, laughter, slowed sense of time, impaired judgment, social withdrawal, appetite, dry mouth, conjunctival injection, hallucinations, anxiety, paranoia, ↓ motivation	Irritability, anxiety, ↓ appetite, insomnia
Bath salts (synthetic cathinones)	Stimulant drug that causes agitation, combativeness, delirium, and psychosis that may last for weeks; not detected on routine urine toxicology screens	Anxiety, depression, insomnia
Gamma-hydroxybutyric acid (GHB)	Hypotension, bradycardia, respiratory depression, disinhibition, ↑ libido, seizures	Irritability, anxiety, tremor, autonomic instability
MDMA (ecstasy)	Amphetamine derivative with hallucinogenic properties; popular at dance parties or "raves" Intoxication: HTN, euphoria, perceptual changes, bruxism, hyperthermia, heat exhaustion, hyponatremia; may also precipitate serotonin syndrome	Depression, anxiety, difficulty concentrating

DTs, Delirium tremens; *HTN*, hypertension; *MPTP*, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; *NSAIDs*, nonsteroidal anti-inflammatory drugs.

ALCOHOL USE DISORDER

Occurs more often in males (4:1) and in those 21 to 34 years of age, although the incidence in females is rising. Alcohol use disorder is associated with a positive family history.

History/PE

See Table 2.13-17 for the symptoms of intoxication and withdrawal. The physician should look for palmar erythema or telangiectasias and for other signs and symptoms of end-organ complications. Patients often present with sleep disturbances or anxiety symptoms caused by mild withdrawal.

Diagnosis

- Screening can be done with the CAGE questionnaire. The physician should monitor vital signs for evidence of withdrawal.
- Labs may reveal ↑ LFTs (classically aspartate aminotransferase [AST]: alanine aminotransferase [ALT] ratio >2:1), ↑ lactate dehydrogenase (LDH), ↑ carbohydrate-deficient transferrin, and ↑ mean corpuscular volume.

MNEMONIC

CAGE questionnaire:

1. Have you ever felt the need to **C**ut down on your drinking?
2. Have you ever felt **A**nnoyed by criticism of your drinking?
3. Have you ever felt **G**uilty about drinking?
4. Have you ever had to take a morning **E**ye opener?

More than one "yes" answer makes alcohol use disorder likely.

Treatment

- **Abstinence:**
  - **Best initial treatment:** Naltrexone (μ-opioid receptor blocker) ↓ cravings; can start while patient is still drinking
  - Long-term rehabilitation (eg, Alcoholics Anonymous)
- **Aversion:** Disulfiram (acetaldehyde dehydrogenase inhibitor): Produces an unpleasant response (eg, flushing, nausea, vertigo, palpitations) when EtOH is consumed

KEY FACT

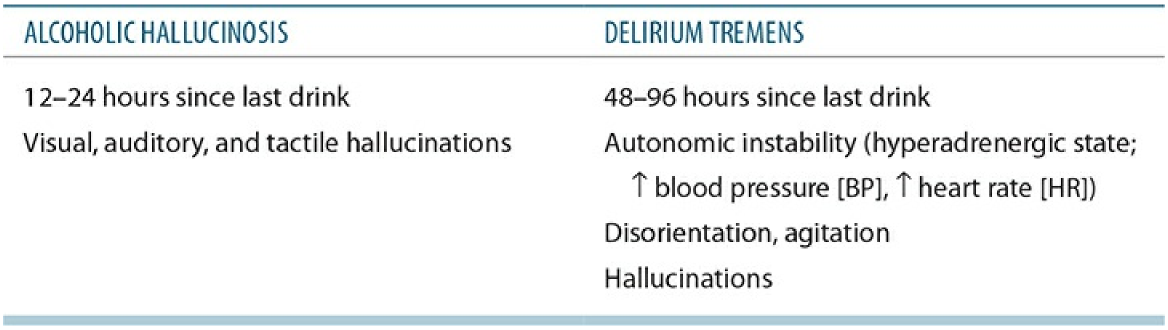
Naltrexone is a first-line pharmacotherapy to reduce the craving for alcohol. It works by blocking the μ-opioid receptor and can be given to patients who are still drinking.

- **Withdrawal:**
  - Stabilization of vital signs; correction of electrolyte abnormalities
  - Thiamine (administer before glucose to prevent Wernicke encephalopathy), glucose, and folic acid
  - Medium-length benzodiazepine taper (eg, lorazepam, diazepam, chlordiazepoxide)
  - Addition of haloperidol for hallucinations and psychotic symptoms

Complications

- Gastritis (gastrointestinal [GI] bleeds, ulcers), varices, or Mallory-Weiss tears
- Pancreatitis, liver disease, delirium tremens (DTs), alcoholic hallucinosis (see Table 2.13-18, Fig. 2.13-2), peripheral neuropathy, Wernicke encephalopathy, Korsakoff psychosis, fetal alcohol syndrome, cardiomyopathy, anemia, aspiration pneumonia, ↑ risk for sustaining trauma (eg, subdural hematoma)

TABLE 2.13-18. **Alcoholic Hallucinosis vs Delirium Tremens**



ALCOHOLIC HALLUCINOSIS	DELIRIUM TREMENS
12–24 hours since last drink	48–96 hours since last drink
Visual, auditory, and tactile hallucinations	Autonomic instability (hyperadrenergic state; ↑ blood pressure [BP], ↑ heart rate [HR])
	Disorientation, agitation
	Hallucinations

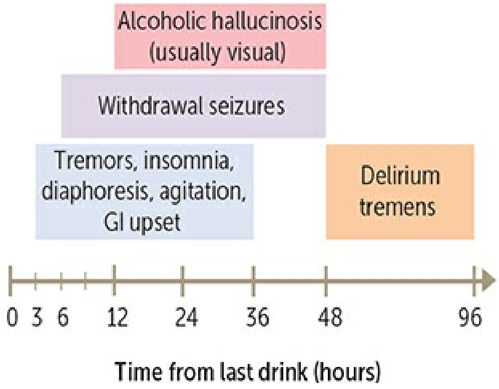
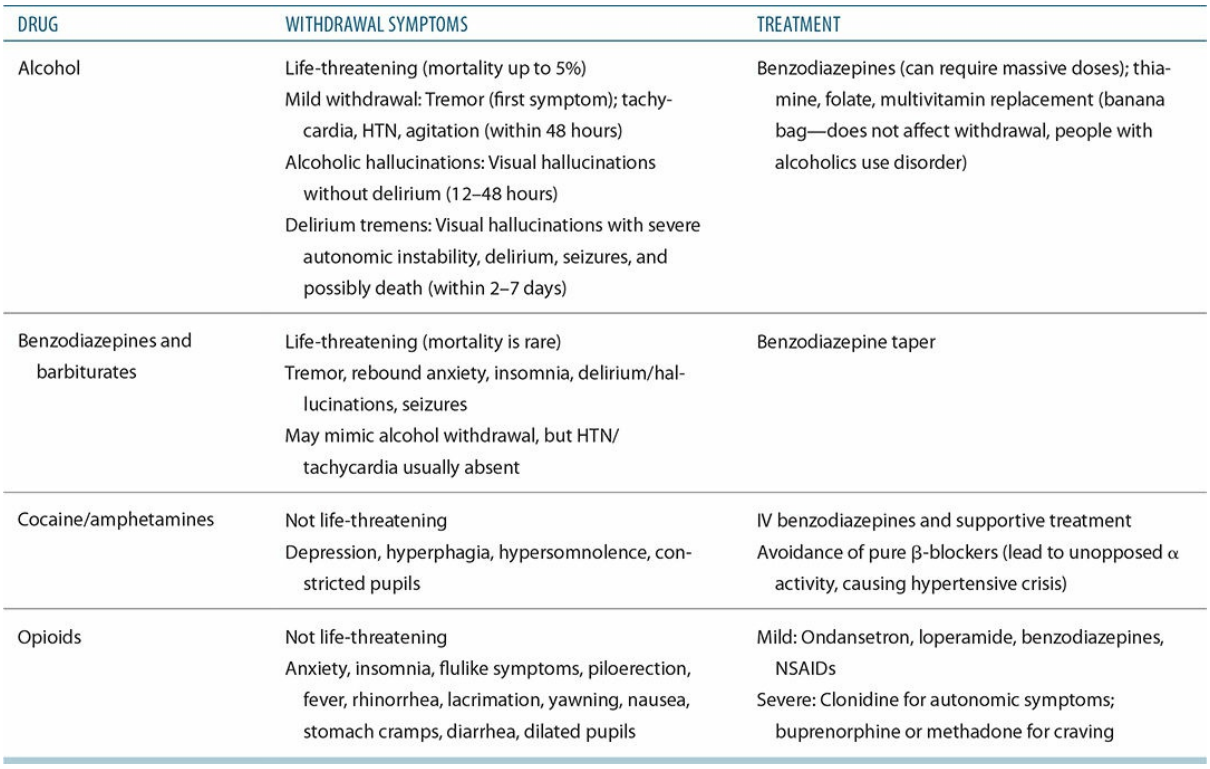


FIGURE 2.13-2. **Alcohol withdrawal timeline.** Alcohol withdrawal can have overlapping symptoms. Time from last drink is important to delineate the type of withdrawal and subsequent management. (Reproduced with permission from USMLE-Rx.com.)

MANAGEMENT OF DRUG WITHDRAWAL

Table 2.13-19 summarizes common drug withdrawal symptoms and treatment.

TABLE 2.13-19. **Symptoms and Treatment of Drug Withdrawal**



DRUG	WITHDRAWAL SYMPTOMS	TREATMENT
Alcohol	Life-threatening (mortality up to 5%) Mild withdrawal: Tremor (first symptom); tachycardia, HTN, agitation (within 48 hours) Alcoholic hallucinations: Visual hallucinations without delirium (12–48 hours) Delirium tremens: Visual hallucinations with severe autonomic instability, delirium, seizures, and possibly death (within 2–7 days)	Benzodiazepines (can require massive doses); thiamine, folate, multivitamin replacement (banana bag—does not affect withdrawal, people with alcoholics use disorder)
Benzodiazepines and barbiturates	Life-threatening (mortality is rare) Tremor, rebound anxiety, insomnia, delirium/hallucinations, seizures May mimic alcohol withdrawal, but HTN/tachycardia usually absent	Benzodiazepine taper
Cocaine/amphetamines	Not life-threatening Depression, hyperphagia, hypersomnolence, constricted pupils	IV benzodiazepines and supportive treatment Avoidance of pure β-blockers (lead to unopposed α activity, causing hypertensive crisis)
Opioids	Not life-threatening Anxiety, insomnia, flulike symptoms, piloerection, fever, rhinorrhea, lacrimation, yawning, nausea, stomach cramps, diarrhea, dilated pupils	Mild: Ondansetron, loperamide, benzodiazepines, NSAIDs Severe: Clonidine for autonomic symptoms; buprenorphine or methadone for craving

KEY FACT

Neonatal abstinence syndrome occurs when a neonate suffers symptoms of substance withdrawal because of in utero exposure to that substance on a consistent basis.

EATING DISORDERS

ANOREXIA NERVOSA

Risk factors include female sex, low self-esteem, and high socioeconomic status. Associated with OCD; MDD; anxiety; and careers/hobbies such as modeling, gymnastics, ballet, and running

History/PE

- Patients are often perfectionists and high achieving. They have a distorted body image and fear of gaining weight. Anorexia nervosa is divided into two subtypes:
  - **Restrictive:** Severe restriction of food intake is primary method of weight loss.
  - **Binge eating/purging:** Food intake is compensated by purging (eg, excessive exercise, vomiting, laxative/diuretic abuse).
- **Signs and symptoms:** Cachexia, body mass index (BMI) <18.5 kg/m^2, lanugo, dry skin, bradycardia, lethargy, hypotension, cold intolerance, and hypothermia (as low as 35°C [95°F]).
- See Table 2.13-20 to differentiate anorexia nervosa from bulimia nervosa.

TABLE 2.13-20. **Anorexia Nervosa vs Bulimia Nervosa**

CHARACTERISTIC	ANOREXIA NERVOSA	BULIMIA NERVOSA
Presentation	Persistent restriction of caloric intake resulting in low body weight; intense fear of gaining weight; distorted body image (patients perceive themselves as overweight or obese)	Episodes of binge eating followed by compensatory behaviors (eg, purging, fasting, excessive exercise) Episodes occur at least once a week for ≥3 months
Weight	Patients are underweight (BMI <18.5 kg/m²)	Patients are of normal weight or are overweight (BMI >18.5 kg/m²)
Attitude toward illness	Patients are typically not distressed by their illness and may thus be resistant to treatment	Patients are typically distressed about their symptoms and are thus easier to treat
Treatment	Monitor calorie intake and weight gain; hospitalize if necessary Watch for refeeding syndrome (electrolyte abnormalities [↓ phosphate], arrhythmias, respiratory failure, and seizures after sudden increase in caloric intake) Psychotherapy: Address maladaptive family dynamics Antidepressants (SSRIs): Note that these are not effective until weight is restored Treat comorbidities; avoid bupropion because of risk for seizure	Psychotherapy ± antidepressants (SSRIs) Treat comorbidities; avoid bupropion because of risk for seizure

Diagnosis

- Measure height and weight; check BMI; check CBC, electrolytes, endocrine levels, and ECG.
- Perform a psychiatric evaluation to screen patients for comorbid conditions.

Treatment

See Table 2.13-20.

Complications

See Table 2.13-20 and Table 2.13-21. Mortality from suicide or medical complications is >10%.

TABLE 2.13-21. Medical Complications of Eating Disorders

CONSTITUTIONAL	CARDIAC	GASTROINTESTINAL	GENITOURINARY	OTHER
Cachexia Hypothermia Fatigue Electrolyte abnormalities (hypokalemia, pH abnormalities)	Arrhythmias Sudden death Hypotension Bradycardia Prolonged QT interval	Dental erosions and decay Abdominal pain Delayed gastric emptying	Amenorrhea Nephrolithiasis	Dermatologic: Lanugo Hematologic: Leukopenia Neurologic: Seizures Musculoskeletal: Osteoporosis, stress fractures

BULIMIA NERVOSA

Eating disorder characterized by recurrent episodes of binge eating and compensatory purging behavior (eg, vomiting, laxative/diuretic abuse, excessive exercise). More common in females; associated with low self-esteem, mood disorders, and OCD.

History/PE

- Patients often have a long history of other comorbid psychiatric conditions (eg, anxiety, depression) and are concerned about their behaviors.

- **Signs:** Dental enamel erosion, enlarged parotid glands, scars on the dorsal hand surfaces (if there is a history of repeated induced vomiting), and BMI >18.5 kg/m^2 are signs of bulimia nervosa.
- See Table 2.13-20 to differentiate anorexia nervosa from bulimia nervosa.

Treatment

See Table 2.13-20.

Complications

See Table 2.13-21 for a summary of complications related to eating disorders.

SEXUAL DISORDERS

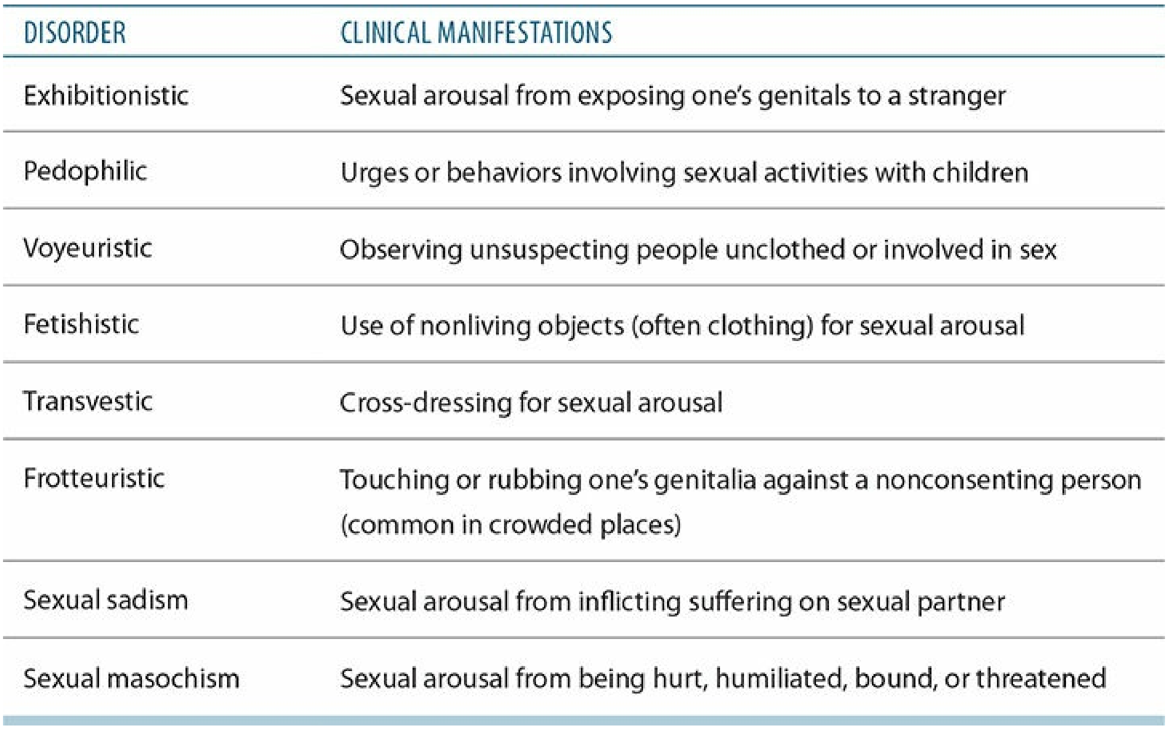
SEXUAL CHANGES WITH AGING

- Interest in sexual activity usually does not ↓ with aging.
- Males usually require ↑ stimulation of the genitalia for longer periods of time to reach orgasm; intensity of orgasm ↓, and the length of the refractory period before the next orgasm ↑.
- In females, estrogen levels ↓ after menopause, leading to vaginal dryness and thinning, which may result in discomfort during coitus. The patient may be treated with hormone replacement therapy, estrogen vaginal suppositories, or other vaginal creams.

PARAPHILIC DISORDERS

- Preoccupation with or engagement in unusual sexual fantasies, urges, or behaviors for >6 months with clinically significant impairment of one's life. There are eight classified disorders, characterized by disordered courtship (voyeurism, exhibitionism, and frotteurism), disordered preferences (pedophilia, transvestic fetishism, fetishism), and pleasure in inflicting/receiving pain (sadism, masochism). See Table 2.13-22.

TABLE 2.13-22. Features of Common Paraphilic Disorders



DISORDER	CLINICAL MANIFESTATIONS
Exhibitionistic	Sexual arousal from exposing one's genitals to a stranger
Pedophilic	Urges or behaviors involving sexual activities with children
Voyeuristic	Observing unsuspecting people unclothed or involved in sex
Fetishistic	Use of nonliving objects (often clothing) for sexual arousal
Transvestic	Cross-dressing for sexual arousal
Frotteuristic	Touching or rubbing one's genitalia against a nonconsenting person (common in crowded places)
Sexual sadism	Sexual arousal from inflicting suffering on sexual partner
Sexual masochism	Sexual arousal from being hurt, humiliated, bound, or threatened

- ***Tx:*** Includes insight-oriented psychotherapy and behavioral therapy. Antiandrogens (eg, a medroxyprogesterone injection) have been used for hypersexual paraphilic activity.

GENDER DYSPHORIA

Significant incongruence between one's gender identity and one's gender assigned at birth, lasting >6 months and leading to persistent distress. Individuals experience marked discomfort with assigned gender, which interferes with social, academic, and other areas of function. More common in males than females.

History/PE

More common in males than in females. Gender dysphoria is associated with depression, anxiety, substance abuse, and personality disorders.

- Some individuals who are transgender will experience gender dysphoria. Nonconformity to one's assigned gender itself is not a mental disorder. Gender dysphoria is associated with depression, anxiety, substance abuse, and personality disorders.

Treatment

- Address comorbid psychiatric conditions. If the patient is interested, discuss options for gender-affirming surgery or hormonal treatment.
- In teens, hormone suppression therapy can be offered to delay puberty, but this decision should be made with support from family, if possible. One should also assess safety and multidisciplinary specialist services.

SEXUAL DYSFUNCTION

History/PE

- Problems in sexual arousal, desire, or orgasm or pain with sexual intercourse

- **Prevalence:** 30%; one-third of cases are attributable to biologic factors, and another third to psychological factors

Treatment

Depends on the condition. Pharmacologic strategies include phosphodiesterase type 5 (PDE5) inhibitors (eg, sildenafil, tadalafil). If dysfunction is caused by antidepressants (SSRIs), the physician can institute a switch to bupropion. Psychotherapeutic strategies include sensate focusing.

SLEEP DISORDERS

Up to one-third of all American adults suffer from some type of sleep disorder during their lives. Dyssomnia describes any condition that leads to a disturbance in the normal rhythm or pattern of sleep. Insomnia is the most common example. Risk factors include female sex, the presence of mental and medical disorders, substance abuse, and advanced age.

Normal age-related sleep changes include more frequent waking, decreased total time asleep, and increased napping.

PRIMARY INSOMNIA

Affects up to 30% of the general population; causes sleep disturbance that is not attributable to physical or mental conditions. Insomnia is often exacerbated by anxiety, and patients may become preoccupied with getting enough sleep.

History/PE

Patients present with a history of nonrestorative sleep or difficulty initiating or maintaining sleep that is present at least three times per week for 1 month.

Treatment

- **Best initial treatment:** Initiate good sleep hygiene measures.
- **Next best treatment:** Psychotherapy, specifically CBT for insomnia (CBTi). Pharmacotherapy can be initiated with care for short periods of time (<2 weeks). Pharmacologic agents include diphenhydramine, zolpidem, zaleplon, and trazodone.

KEY FACT

Sleep hygiene measures—stimulus control therapy to reestablish a 24-hour sleep/wake cycle:

- Establish a sleep schedule
- Limit caffeine intake
- Avoid naps
- Take warm baths in the evening
- Use the bedroom for sleep and sexual activity only
- Exercise early in the day
- Employ relaxation techniques
- Avoid large meals near bedtime

PRIMARY HYPERSOMNIA

Diagnosis

Diagnosed when a patient complains of excessive daytime sleepiness or nighttime sleep that occurs for >1 month. The excessive somnolence cannot be attributable to medical or mental illness, medications, poor sleep hygiene, insufficient sleep, or narcolepsy.

Treatment

- **Best initial treatment:** CNS stimulants (eg, amphetamines)
- Antidepressants such as SSRIs may be useful in some patients

NARCOLEPSY

Onset typically occurs by young adulthood, generally before 30 years of age. Some forms of narcolepsy may have a genetic component.

Diagnosis

- Manifestations include excessive daytime somnolence and ↓ rapid eye movement (REM) sleep latency at least three times a week for at least 3 months. Hypocretin deficiency (confirmed by cerebrospinal fluid [CSF] sampling) is also diagnostic of this condition. Sleep attacks are the classic symptom; patients cannot avoid falling asleep.
- Characteristic excessive sleepiness may be associated with the following:
  - **Cataplexy:** Sudden loss of muscle tone that leads to collapse
  - **Hypnagogic hallucinations:** Occur as the patient is falling asleep
  - **Hypnopompic hallucinations:** Occur as the patient awakens
  - **Sleep paralysis:** Brief paralysis upon awakening

MNEMONIC

Hypna**GO**gic = hallucinations while **GO**ing to bed
Hypno**POMP**ic = hallucinations while **POMP**ing out of bed

Treatment

A regimen of scheduled daily naps plus stimulant drugs such as amphetamines or modafinil; SSRIs for cataplexy.

Sleep Apnea

- Sleep apnea occurs secondary to disturbances in breathing during sleep that lead to excessive daytime somnolence and sleep disruption. Etiologies can be either central or peripheral.
  - **Central sleep apnea (CSA):** A condition in which both airflow and respiratory effort cease. CSA is linked to morning headaches, mood changes, and repeated awakenings during the night.
  - **Obstructive sleep apnea (OSA):** A condition in which airflow ceases as a result of obstruction along the respiratory passages. OSA is strongly associated with snoring.

    Risk factors: Male sex, obesity, prior upper airway surgeries, a deviated nasal septum, a large uvula or tongue, and retrognathia (recession of the mandible).
  - In both forms, arousal results in cessation of the apneic event.
- Sleep apnea is associated with sudden death in infants and older adults, headaches, depression, ↑ systolic blood pressure (BP), and pulmonary hypertension.

Diagnosis

Sleep study (polysomnography) to document the number of arousals, obstructions, and episodes of ↓ O_2 saturation; distinguish OSA from CSA; and identify possible movement disorders, seizures, or other sleep disorders.

Treatment

- **OSA:** Nasal continuous positive airway pressure (CPAP). Weight loss if obese. In children, most cases are caused by tonsillar/adenoidal hypertrophy, which is corrected surgically.
- **CSA:** Mechanical ventilation (eg, bilevel positive airway pressure [BiPAP]) with a backup rate for severe cases.

CIRCADIAN RHYTHM SLEEP DISORDER

A spectrum of disorders characterized by a misalignment between desired and actual sleep periods. Subtypes include jet lag, shift work, delayed sleep phase (“night owls”), advanced sleep phase (“early birds”), and unspecified causes.

Treatment

- Jet-lag type usually resolves within 2 to 7 days without specific treatment.
- Shift-work and delayed sleep-phase types may respond to light therapy. Modafinil is approved for shift-work sleep disorder.
- Oral melatonin may be useful if given 30 minutes before the desired bedtime.

Q

A 57-year-old morbidly obese man presents to his physician with concerns about ↑ daytime sleepiness and ↓ work productivity. His wife adds that he has excessive snoring that sounds like “the snort of a steam engine.” What long-term complications are of concern for this patient?

SOMATIC SYMPTOM AND RELATED DISORDERS

SOMATIC SYMPTOM DISORDER

Patients often present with excessive thoughts, anxiety, and behaviors driven by the presence of somatic symptoms that are distressing and negatively affect daily life. Somatic symptom disorder may occur with or without any medical illness present. High health care utilization is often present. Disorder may present with multiple recurrent somatic symptoms that may be specific (eg, localized pain) or nonspecific (eg, fatigue). Even normal bodily symptoms can be perceived as unduly threatening, even when there is evidence to the contrary.

Treatment

- Scheduling regular appointments with one clinician as primary caregiver
- Avoiding unnecessary diagnostics but legitimizing symptoms
- Psychotherapy focused on reducing psychosocial stressors

ILLNESS ANXIETY DISORDER

Formerly known as hypochondria. For at least 6 months, patients have anxiety about and preoccupation with acquiring a serious medical illness despite having no somatic symptoms (or mild somatic symptoms), a normal physical examination, negative tests, and reassurance from a health care provider. The patient's preoccupation with illness is not better explained by another disorder. In addition to the aforementioned, patients must have one of the following: excessive health behaviors (eg, repeated checking for signs of an illness) or maladaptive avoidance of situations (eg, health care settings, visiting sick family members).

KEY FACT

Psychogenic/nonepileptic spells can co-occur with a seizure disorder.

Treatment

- CBT (first line)
- Another type of psychotherapy (second line)
- Antidepressant medication (third line)

CONVERSION DISORDER

Also known as functional neurologic symptom disorder. Characterized by symptoms or deficits of voluntary motor or sensory function (eg, blindness, seizurelike movements, paralysis) incompatible with medical processes. Close temporal relationship to stress or intense emotion.

Diagnosis

- Symptoms unexplained by other medical or neurologic causes
- Signs during physical examination suggesting nonorganic cause of symptoms:
  - Presence of Hoover sign (extension of affected leg when asked to raise the unaffected contralateral leg) when attempting to rule out leg paralysis
  - Eyes closed and resistant to opening during seizure; negative simultaneous EEG
  - Disappearance of tremors with distraction
- **La belle indifference:** Patients are strangely indifferent to their symptoms; commonly associated but not required for the diagnosis

A

This patient has obstructive sleep apnea. Serious consequences include leg swelling, hypertension, cor pulmonale, stroke, and clinical depression.

Treatment

- Psychotherapy, physical therapy (PT)/occupation therapy (OT), treating comorbid psychiatric issues (anxiety, depression, trauma)
- Goal: Improve function

FACTITIOUS DISORDERS AND MALINGERING

Diagnosis

- **Factitious disorder (formerly Munchausen syndrome):** Characterized by the fabrication of symptoms or self-injury to assume the sick role (primary gain)
- **Factitious disorder imposed on another (formerly Munchausen by proxy):** Caregiver exaggerates or falsifies medical/psychiatric symptoms or intentionally induces illness in someone else to receive benefit by taking on the role of concerned caregiver
- **Malingering:** Patients intentionally cause or feign symptoms for secondary gain (eg, financial, housing, legal)

KEY FACT

Factitious disorders and malingering are distinct from somatoform disorders in that they involve conscious and intentional processes.

Treatment

- Psychotherapy
- Minimal diagnostics and treatment to avoid reinforcement of behaviors
- Contacting appropriate legal authorities (factitious disorder imposed on another)

SEXUAL AND PHYSICAL ABUSE

- Most frequently affects females <35 years of age who:
  - Are experiencing marital discord and have a personal history of, or a partner with, substance abuse
  - Are pregnant, have low socioeconomic status, or have obtained a restraining order
- Victims of childhood abuse are more likely to become adult victims of abuse

History/PE

- Patients typically have multiple somatic complaints, frequent emergency department visits, and unexplained injuries with delayed medical treatment. They may also avoid eye contact or act afraid or hostile.
- Children may exhibit precocious sexual behavior, genital or anal trauma, sexually transmitted diseases (STDs), UTIs, and/or psychiatric/behavioral problems (see Pediatrics chapter).
- Other clues include a partner who answers questions for the patient or refuses to leave the examination room.

Treatment

- Perform a screening assessment of the patient's safety domestically and in their close personal relationships.
- Provide medical care, emotional support, and counseling.
- Educate the patient about support services and refer the patient appropriately.
- Documentation is crucial. Know local laws for reporting suspected child/elder abuse.

KEY FACT

Sexual abusers are usually male and are often known to the victim (and are often family members).

SEXUAL ASSAULT

Any sexual act performed on another individual without their consent.

Diagnostic Evaluation and Testing

- Assessment for physical injury with focus on genital trauma
- Psychological evaluation
- Pregnancy test
- Testing for sexually transmitted infections
  - Smear/culture for chlamydia and gonorrhea
  - Wet mount and culture for trichomonas
  - Consideration of testing for HIV, herpes simplex virus (HSV), hepatitis B virus (HBV), syphilis, and cytomegalovirus (CMV)
- Forensic evaluation with detailed history and samples from buccal mucosa, vagina, rectum, fingernail scraping and clippings, blood samples, and saliva samples
  - Important historical details include contraceptive use, last time of coitus, condom use before the assault, drug or alcohol use, history of STDs, description of the assailant, location and time of the assault, circumstances of the assault (eg, penile penetration, use of condoms, extragenital acts, use or display of weapons), and the patient's actions since the assault (eg, douching, bathing, brushing teeth, urination/defecation, changing clothes).

Postexposure Prophylaxis and Evaluation

- Follow-up medical visit within 1 to 2 weeks
- Ceftriaxone plus azithromycin ± metronidazole for prophylaxis against gonorrhea and chlamydia
- Hepatitis B booster vaccination if unknown vaccination and immune status or if unvaccinated
- HIV: Antiretroviral drug offered within 72 hours of assault; options are tenofovir-emtricitabine + raltegravir
- Human papillomavirus (HPV) vaccination recommended at time of initial evaluation in female survivors ages 9 to 26 years and male survivors ages 9 to 21 years

Contraception

- Emergency contraception: Progestin/antagonist/agonist ulipristal or levonorgestrel or combination ethinyl estradiol and levonorgestrel (Yuzpe regimen)

- Offer for mental health services

MNEMONIC

Risk factors for suicide attempts—

SAD PERSONS

Sex (male)
Age (older)
Depression
Previous attempt (greatest risk)
Ethanol/substance abuse
Rational thinking loss
Sickness (chronic illness)
Organized plan/access to weapons
No spouse
Social support lacking

SUICIDALITY

Accounts for 45,000 deaths per year in the United States; the 10th overall cause of death in the United States. Approximately one suicide occurs every 11 minutes.

- **Risk factors:** Previous suicide attempt (primary risk factor), male sex, >45 years of age, psychiatric disorders (eg, MDD, presence of psychotic symptoms), history of psychiatric hospitalization, history of violent behavior, ethanol or substance abuse, recent severe stressors, poor social support, and a family history of suicide (see **SAD PERSONS** mnemonic).
- Females are more likely to attempt suicide. Men use more lethal methods (eg, firearms) and are more likely to complete suicide.
- Adults aged 45 to 64 have higher rates of death from suicides than other age groups. However, young adults aged 18 to 25 are at higher risk for suicidal thoughts and attempts than other age groups.
- **Protective factors:** Social support, family connectedness, religiosity, pregnancy, and parenthood.

KEY FACT

Suicide is the second leading cause of death (after unintentional injury) among 15- to 24-year-olds in the United States.

Diagnosis

- Perform a comprehensive psychiatric evaluation.
- Ask about family history, previous attempts, ambivalence toward death, and hopelessness.
- Ask directly about suicidal ideation, intent, and plan, and look for available means.

KEY FACT

Emergent inpatient hospitalization is required for patients with suicidal intentions.

Treatment

- A patient who endorses suicidality requires emergent inpatient hospitalization even against their will.
- Suicide risk may increase after antidepressant therapy is initiated and is considered an adverse effect of the medication. There is a black box warning on all antidepressant medications when used in those <24 years of age.

NOTES

HIGH-YIELD FACTS IN

PULMONARY

Obstructive Lung Disease

- ASTHMA
- BRONCHIECTASIS
- CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Restrictive Lung Disease

- INTERSTITIAL LUNG DISEASE
- CRYPTOGENIC ORGANIZING PNEUMONIA
- SYSTEMIC SARCOIDOSIS
- HYPERSENSITIVITY PNEUMONITIS
- PNEUMOCONIOSIS
- EOSINOPHILIC PULMONARY SYNDROMES
- ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Acute Respiratory Failure

- HYPOXEMIA
- ACUTE RESPIRATORY DISTRESS SYNDROME
- MECHANICAL VENTILATION
- CORONAVIRUSES AND COVID-19

Pulmonary Vascular Disease

- PULMONARY HYPERTENSION/COR PULMONALE
- PULMONARY THROMBOEMBOLISM

Neoplasms of the Lungs

- SOLITARY PULMONARY NODULES
- LUNG CANCER

Respiratory Tract Infections

- PNEUMONIA
- INFLUENZA
- ASPERGILLOSIS
- HISTOPLASMOSIS
- COCCIDIOMYCOSIS
- BLASTOMYCOSIS

Mycobacterial Infections

- TUBERCULOSIS
- NONTUBERCULOUS MYCOBACTERIA

Pneumocystis jirovecii Pneumonia

Anthrax

Acute Pharyngitis

Oral Infections
- LUDWIG ANGINA
- ACUTE LYMPHADENITIS

Sinusitis

Hemoptysis

Pleural Disease
- PLEURAL EFFUSION
- PNEUMOTHORAX

Pulmonary Sleep Disorders
- OBSTRUCTIVE SLEEP APNEA
- OBESITY HYPOVENTILATION SYNDROME

Nose and Throat
- RHINITIS
- NASAL POLYPS
- EPISTAXIS
- ADENOTONSILLAR HYPERTROPHY
- ACUTE AND CHRONIC LARYNGITIS
- LARYNGOPHARYNGEAL REFLUX
- BENIGN AND MALIGNANT LARYNGEAL LESIONS

OBSTRUCTIVE LUNG DISEASE

Characterized by airway narrowing or collapse that causes impaired expiration and results in air trapping. Figure 2.14-1 illustrates the role of lung volume measurements in the diagnosis of lung disease; Table 2.14-1 and Figure 2.14-2 contrast obstructive lung disease with restrictive lung disease.

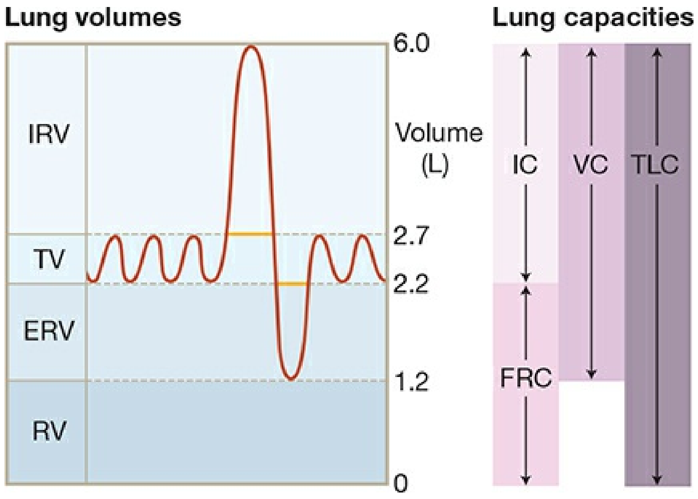


FIGURE 2.14-1. **Lung volumes in the interpretation of pulmonary function tests (PFTs).** Left panel shows lung volumes, and right panel shows lung capacities. *ERV*, Expiratory reserve volume; *FRC*, functional residual capacity; *IC*, inspiratory capacity; *IRV*, inspiratory reserve volume; *RV*, residual volume; *TLC*, total lung capacity; *TV*, total volume; *VC*, vital

capacity. (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.14-1. Obstructive vs Restrictive Lung Disease

TEST	NORMAL	OBSTRUCTIVE	RESTRICTIVE
FEV_1/FVC (FEV_1 %)	>0.70	↓	Normal/↑
FEV_1 (% of predicted)	80%–120%	↓	↓
FVC (% of predicted)	80%–120%	Normal/↓	↓
FRC (% of predicted)	80%–120%	↑	↓
TLC (% of predicted)	80%–120%	↑	↓

FEV1: Forced expiratory volume in 1 second; FRC: functional residual capacity; FVC: forced vital capacity; TLC: total lung capacity.

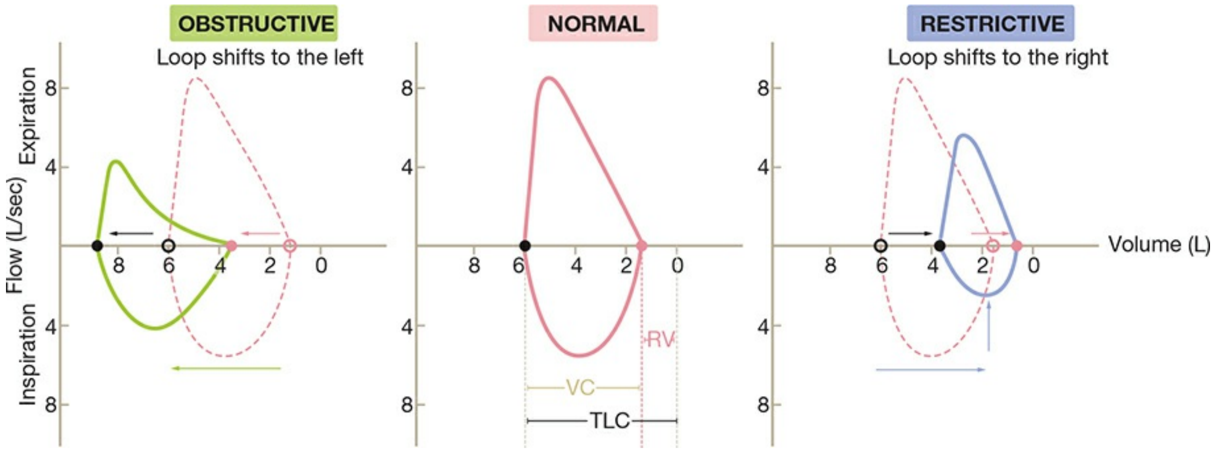


FIGURE 2.14-2. Obstructive vs restrictive lung disease. Shown are typical alterations in lung volumes and capacities in restrictive and obstructive diseases. Normal flow-volume loops shown in center panel. Obstructive lung disease *(left)* causes increased reserve volume and total lung capacity due to air trapping. Restrictive lung disease shows a reduction in all lung volumes due to reduced lung expansion *(right)*. *RV*, Residual volume; *TLC*, total lung capacity; *VC*, vital capacity. (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

FEV_1/FVC ratio <70% suggests obstructive ventilatory defect (eg, asthma, bronchiectasis, COPD).

FEV_1/FVC ratio ≥70% suggests restrictive ventilatory defect (eg, interstitial lung disease, neuromuscular diseases, obesity, scoliosis).

MNEMONIC

Etiologies of obstructive pulmonary disease—

ABCO
Asthma
Bronchiectasis
Chronic obstructive pulmonary disease (**C**OPD)/**C**ystic fibrosis
Obstruction (tracheal or bronchial)

ASTHMA

Reversible airway obstruction secondary to bronchial hyperreactivity, airway inflammation, mucus plugging, and smooth muscle hypertrophy. Most often diagnosed in childhood or early adulthood but can present later.

KEY FACT

Beware—all that wheezes is not asthma! Other conditions that can cause wheezing are foreign body inhalation, left heart failure (cardiac wheezing), and COPD (ie, anything causing airway constriction).

History/PE

- Usually presents with dry cough, episodic wheezing, dyspnea, and/or chest tightness, often worsening at night or in early morning
- **PE:** Wheezing, prolonged expiration (↓ inspiration/expiration ratio), increased accessory muscle use, tachypnea, tachycardia, and hyperresonance.
- **Signs of severe disease:** ↓ breath sounds, cyanosis, ↓ O_2 saturation, hypercapnia (↑ partial pressure of carbon dioxide in arterial blood [$Pa{CO_2}$]), and pulsus paradoxus

KEY FACT

Asthma should be suspected in children with multiple episodes of croup and upper respiratory tract infections associated with dyspnea. Children with eczema are more likely to develop asthma or allergic rhinitis than those without eczema.

KEY FACT

Asthma triggers include allergens, upper respiratory infections (URIs), cold air, exercise, drugs (eg, aspirin, NSAIDs, β-blockers), and stress in both adults and children.

- **Aspirin-exacerbated respiratory disease:** Samter triad has three clinical features: asthma, chronic rhinosinusitis with nasal polyps, and intolerance to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs; most commonly upper and lower respiratory tract symptoms but occasionally also rash, abdominal pain, or vomiting). Pseudoallergic reaction (not IgE mediated)

KEY FACT

The physician should suspect impending respiratory failure in a patient with severe asthma exacerbation and normal or normalizing $PaCO_2$ and pH.

Diagnosis

- **Best initial test:** Spirometry/pulmonary function tests (PFTs); obstructive pattern that is reversible with short-acting β_2-agonists (SABAs)
  - Forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) <70%, ↓ FEV_1, normal/↓ FVC, ↑ residual volume (RV) and total lung capacity (TLC), normal/↑ diffusing capacity of the lung for carbon monoxide (DLCO). Increase in FEV_1 ≥12% and >200 mL in FEV_1 with SABA (albuterol). PFTs are often normal between exacerbations.
- **Methacholine challenge:** Tests for bronchial hyperresponsiveness; useful when PFTs are normal but asthma is still suspected. The methacholine challenge is considered positive with ≥20% decrease in FEV_1. The test is sensitive but not specific.
- **Arterial blood gas (ABG):**
  - Early exacerbation: Respiratory alkalosis is caused by hyperventilation (↓ $PaCO_2$, ↑ pH).
  - Late/severe exacerbation (impending respiratory failure): Respiratory muscle fatigue results in respiratory acidosis caused by inability to ventilate (normalizing $PaCO_2$, normalizing pH, ↓ partial pressure of oxygen in arterial blood [PaO_2]).
- **X-ray of the chest (CXR):** Normal appearance to hyperinflation with flattening of the diaphragm.

KEY FACT

Summary of asthma medications:

- PRN (as needed) medications—short-acting bronchodilators (eg, albuterol)
- Long-term medications—inhaled corticosteroids, long-acting β_2-agonists (eg, salmeterol), long-acting muscarinic antagonists (LAMAs), leukotriene antagonists (eg, montelukast), and PO (by mouth) corticosteroids.

MNEMONIC

Medications for asthma exacerbations—

ASTHMA

Albuterol (bronchodilator)
Steroids (anti-inflammatory)
Theophylline (rarely used bronchodilator due to narrow therapeutic index)
Humidified O_2 (in hypoxemic patients)
Magnesium (bronchodilator used in severe exacerbations)
Anticholinergics (bronchodilator)

Treatment

In general, avoidance of allergens or any potential triggers. See Tables 2.14-2 and 2.14-3 for asthma medications and management guidelines.

TABLE 2.14-2. **Common Asthma Medications and Their Mechanisms**

DRUG	MECHANISM OF ACTION
β_2-agonists	Albuterol: Short-acting (SABA); relaxes bronchial smooth muscle (β_2-adrenoceptors) Salmeterol + inhaled corticosteroids (ICS): Long-acting (LABA) agent for maintenance therapy Formoterol + ICS: Maintenance and reliever therapy (MART) with both short-acting and long-acting effects
Corticosteroids	Inhaled corticosteroids: First-line treatment for long-term control of asthma Beclomethasone, prednisone: Inhibit the synthesis of cytokines
Muscarinic antagonists	Ipratropium: Short-acting muscarinic antagonist (SAMA); competitively blocks muscarinic receptors, preventing bronchoconstriction Tiotropium: Long-acting muscarinic antagonist (LAMA)
Methylxanthines	Theophylline: Causes bronchodilation by inhibiting phosphodiesterase, thereby ↓ cAMP hydrolysis and cAMP levels; limited usage because of narrow therapeutic-toxic index (cardiotoxicity, neurotoxicity)
Cromolyn	Prevents the release of vasoactive mediators from mast cells Useful for exercise-induced bronchospasm Effective only for the maintenance of asthma; not effective during an acute attack; toxicity is rare
Antileukotrienes	Zileuton: A 5-lipoxygenase pathway inhibitor; blocks conversion of arachidonic acid to leukotrienes Montelukast, zafirlukast: Block leukotriene receptors
Anti-IgE	Omalizumab: Monoclonal antibody against IgE; inhibits IgE binding to IgE receptor (FcεRI) on mast cells; used in patients with allergic asthma and high baseline IgE level
Anti-IL-5/anti-IL-5R	Mepolizumab, reslizumab: Monoclonal antibody against interleukin (IL)-5 (potent chemoattractant for eosinophils) Benralizumab: Monoclonal antibody against IL-5 receptor, which blocks binding of IL-5, resulting in inhibition of eosinophil differentiation and maturation in bone marrow; refer to Table 2.14-3
Anti-IL-4R	Dupilumab: Binds IL-4 receptor and inhibits IL-4 and IL-13 cytokine-induced responses, thus inhibiting release of inflammatory cytokines, chemokines, and IgE; refer to Table 2.14-3

TABLE 2.14-3. **Initiation of Asthma Treatment in Adults and Adolescents Aged 12+ Based on Global Initiative for Asthma (GINA) Guidelines**

PREFERRED TRACK[a]				
STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
As-needed low-dose ICS/formoterol	As-needed low-dose ICS/formoterol	Low-dose maintenance ICS/LABA	Medium-/high-dose maintenance ICS/LABA	Addition of LAMA Phenotypic assessment ± anti-IgE, anti-IL-5/5R, anti-IL-4R Consideration of high-dose ICS/LABA

Reliever medication: Low-dose ICS/formoterol as needed for all steps

Criteria for initiation of treatment at various steps:

STEP 1: Symptoms less than two times/month

STEP 2: Symptoms fewer than 4–5 days/week

STEP 3: Symptoms on most days OR on waking more than once a week

STEP 4: Symptoms daily OR on waking more than once a week with low lung function

When to step up ongoing treatment:

Treatment can be stepped up or down along one track or can be switched between tracks[a] according to an individual patient's need.

Before stepping up or down, the physician should check inhaler technique, patient adherence, and environmental exposures and confirm that symptoms are due to asthma.

[a] **Alternate track:** As an alternative, SABA can be taken as needed as a reliever mediation. This can be combined with low-dose ICS as needed (step 1), or low-dose ICS maintenance therapy can be started (step 2). All other add-on medications (steps 3–5) are the same as the preferred track.

- **Acute exacerbation:**
  - O_2, SABA (albuterol is first-line), systemic glucocorticoids. SABA/ipratropium and magnesium can be used in severe exacerbations. Ipratropium should not be used alone in asthma treatment.
  - The physician should consider intubation in severe cases (cyanosis, inability to maintain respiratory effort, altered mental status) or in patients with a Pa_{CO_2} >50 mm Hg or Pa_{O_2} <50 mm Hg.
- **Initiation and adjustment of maintenance therapy:**
  - Initiation of treatment is determined by asthma symptom severity at baseline.
  - Therapy may include a combination of controller medications (which prevent exacerbations, eg, salmeterol + ICS) and reliever medications (which treat exacerbations acutely, eg, albuterol). Certain medications (formoterol + ICS) have both controller and reliever effects.
  - Controller therapy may be stepped up or down in intensity according to patient's needs.

KEY FACT

Corticosteroids inhaled in a **rush** can lead to **thrush!**

KEY FACT

Adults and adolescents diagnosed with asthma, even mild forms, should use ICSs to control airway inflammation. Benefits of low-dose ICSs include improved lung function and reductions in symptoms, severe exacerbations, mortality, and exercise-induced bronchoconstriction.

BRONCHIECTASIS

A disease caused by recurrent cycles of infection and inflammation in the bronchi/bronchioles that leads to fibrosis, remodeling, and permanent dilation of bronchi (see Fig. 2.14-3).

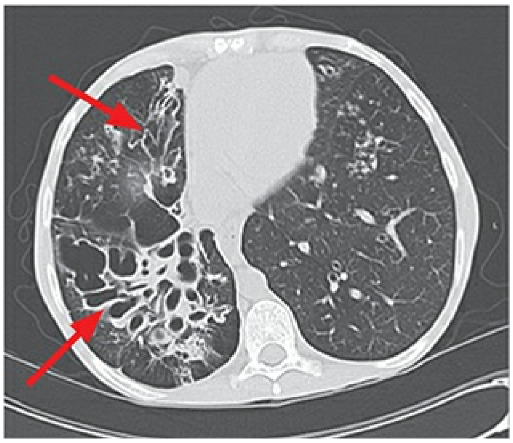


FIGURE 2.14-3. **Bronchiectasis.** CT of the chest demonstrates markedly dilated and thick-walled airways *(arrows)* consistent with bronchiectasis in this cystic fibrosis (CF) patient. (Reproduced with permission from USMLE-Rx.com.)

History/PE

- Presents with chronic productive cough accompanied by frequent bouts of yellow or green sputum production, dyspnea, and possible hemoptysis and halitosis
- Associated with a history of cystic fibrosis (CF), pulmonary infections (eg, *Pseudomonas*, atypical mycobacteria), allergic bronchopulmonary aspergillosis, hypersensitivity, immunodeficiency, localized airway obstruction, aspiration, autoimmune disease, or inflammatory bowel disease (IBD)
- PE: Reveals rales, wheezes, rhonchi, purulent mucus, and occasional hemoptysis

Diagnosis

- **CXR:** Shows ↑ bronchovascular markings and tram lines (parallel lines outlining dilated bronchi as a result of peribronchial inflammation and fibrosis).
- **Most accurate test:** High-resolution CT. Dilated airways (ie, larger than pulmonary arteries) and ballooned cysts are seen at the end of the bronchus (mostly lower lobes).
- **Spirometry/PFTs:** Obstructive pattern with ↓ FEV_1/FVC ratio.
- **Additional tests to identify underlying etiology:** Depends on clinical suspicion. Sputum microscopy and culture may reveal chronic infection (eg, *Pseudomonas*, *Escherichia coli*, tuberculosis) or suggest allergic bronchopulmonary aspergillosis (ie, presence of eosinophils or hyphae). α_1-Antitrypsin levels can rule out deficiency. Sweat chloride and/or genetic testing for *CFTR* mutations may suggest CF. Rheumatoid factor (RF), antinuclear antibody (ANA), or other screening tests for autoimmune disease may also be considered.

Q

A 10-year-old child with a history of asthma on daily fluticasone has been using an albuterol inhaler once a day as needed for several weeks. What changes should be made to the current regimen?

Treatment

- **Medications:** Antibiotics for exacerbations (↓ bacterial load and airway/systematic inflammatory mediators)
  - **Empiric therapy:** Respiratory fluoroquinolone (levofloxacin, moxifloxacin)
  - Tailoring of treatment to sputum culture results, if available
  - **Allergic bronchopulmonary aspergillosis (ABPA):** Systemic glucocorticoids and antifungals (voriconazole, itraconazole)
- **Lifestyle:** Bronchopulmonary hygiene (cough promotion, postural drainage, chest physiotherapy).
- **Surgery:** Consideration of lobectomy for localized disease or lung transplantation for severe disease.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

A disease with ↓ lung function associated with airflow obstruction. Can be divided into two major subtypes:

- **Chronic bronchitis:** Productive cough for >3 months per year for 2 consecutive years (clinical diagnosis)

- **Emphysema:** Destruction and dilation of structures distal to the terminal bronchioles (pathologic diagnosis) that may be secondary to smoking (centrilobular) or to α_1-antitrypsin deficiency (panlobular)

KEY FACT

In patients with COPD and chronic hypercapnia, excess supplemental oxygen can decrease ventilatory drive, resulting in worsening hypercapnia and respiratory acidosis.

KEY FACT

Consider α_1-antitrypsin deficiency in a patient who is <60 years of age, has a family history of COPD, has minimal or no smoking history, has liver disease, and has basilar-predominant COPD.

History/PE

- Symptoms are minimal or nonspecific until the disease is advanced.
- The clinical spectrum is shown in Table 2.14-4 (most patients are a combination of the two phenotypes).

TABLE 2.14-4. **COPD Subtypes: Emphysema and Chronic Bronchitis**

COPD TYPE	DEFINITION	APPEARANCE	ACID-BASE STATUS
Emphysema "Pink puffer"	Terminal airway destruction and dilation	Thin, wasted appearance with pursed lips, minimal cough	Late hypercarbia/hypoxia (hence pink)
Chronic bronchitis "Blue bloater"	Productive cough >3 months for 2 years	Overweight, edematous	Early hypercarbia/hypoxia (hence blue)

- **Symptoms:** Classic barrel chest, use of accessory chest muscles, jugular vein distention (JVD), end-expiratory wheezing, dyspnea on exertion, and muffled breath sounds.
- **ABGs:** Hypoxemia with acute or chronic respiratory acidosis (↑ PaCO_2).
- **Gram stain and sputum culture:** Considered if bacterial infection is suspected (eg, fever, productive cough, new infiltrate on CXR).

KEY FACT

Supplemental O_2 and smoking cessation are the only interventions proven to improve survival in patients with COPD.

Diagnosis

- **Best initial test:** Spirometry (PFTs); obstructive pattern that is nonreversible with SABA.

- FEV$_1$/FVC <70%, ↓ FEV$_1$, normal/↓ FVC, ↑ RV and TLC; minimal (<12%) to no change in FEV$_1$ with SABA (albuterol)
- ↓ DLCO (emphysema or late-stage COPD); normal DLCO (chronic bronchitis)

A

This child has moderate persistent asthma with daily symptoms. The patient will benefit from an inhaled corticosteroid and a long-acting β_2-agonist, such as salmeterol, for prevention of symptoms.

- **CXR:** Hyperinflated lungs, ↓ lung markings with flat diaphragms, and a thin-appearing heart and mediastinum are sometimes seen. Parenchymal bullae or subpleural blebs are also seen (see Fig. 2.14-4).

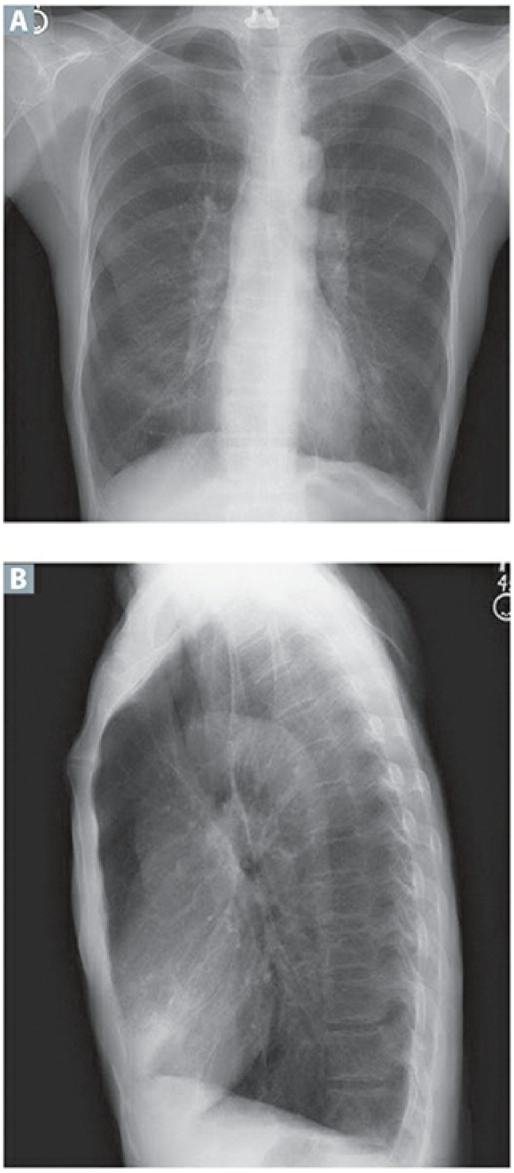


FIGURE 2.14-4. **COPD. (A)** Posteroanterior (PA) and **(B)** lateral radiographs of a patient with emphysema show hyperinflation with large lung volumes, flattening of the diaphragm, and minimal peripheral vascular markings. (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

Treatments for acute asthma and COPD exacerbations both involve β_2-agonists and corticosteroids. During an acute COPD exacerbation, antibiotics may also be given. During an acute asthma exacerbation, magnesium can be given.

Treatment

See Table 2.14-5.

TABLE 2.14-5. COPD Treatment

	TREATMENT
Acute exacerbation	Supplemental O$_2$ (titrate saturation of peripheral oxygen [titrate O$_2$] saturation to 88%–92%) Inhaled bronchodilators: SABA (albuterol) and anticholinergics (ipratropium) Systemic corticosteroids (prednisone) Addition of antibiotics if two or more cardinal symptoms: ■ ↑ dyspnea ■ ↑ cough ■ Sputum production (change from baseline) Severe exacerbations (respiratory failure, severe hypoxemia or respiratory acidosis, altered mental status): ■ Noninvasive positive-pressure ventilation (NPPV) with bilevel positive airway pressure (BiPAP) first. (Note: Increased secretions, facial trauma/burns [poor mask seal], risk of aspiration [eg, due to altered mental status] are contraindications to NPPV.) ■ If NPPV fails, next step: Endotracheal intubation.
Chronic COPD (see Fig. 2.14-5)	Lifestyle modifications: Smoking cessation Vaccines: Pneumococcal vaccine, influenza vaccine (PPSV23 = polysaccharide; PCV13, 15, 20 = conjugate) ■ 19–64 years of age: PCV20 alone or PCV15 + PPSV23 ■ ≥65 years of age: PCV20 alone or PCV15 + PPSV23 ■ All ages: Influenza vaccine annually Inhaled bronchodilators: SABA (albuterol), LABA (salmeterol), anticholinergics (ipratropium, tiotropium) If two or more exacerbations per year, consideration for adding ICS Long-term oxygen therapy (LTOT) ■ LTOT is indicated if Spo$_2$ $\leq$88% or Pao$_2$ $\leq$55 mm Hg in most patients. In those with cor pulmonale, right heart failure, or polycythemia (hematocrit [Hct] >55%), LTOT is indicated when Spo$_2$ $\leq$89% or Pao$_2$ $\leq$59 mm Hg. ■ Supplemental O$_2$ can worsen hypercapnia. The goal oxygen saturation is 90%–93%.

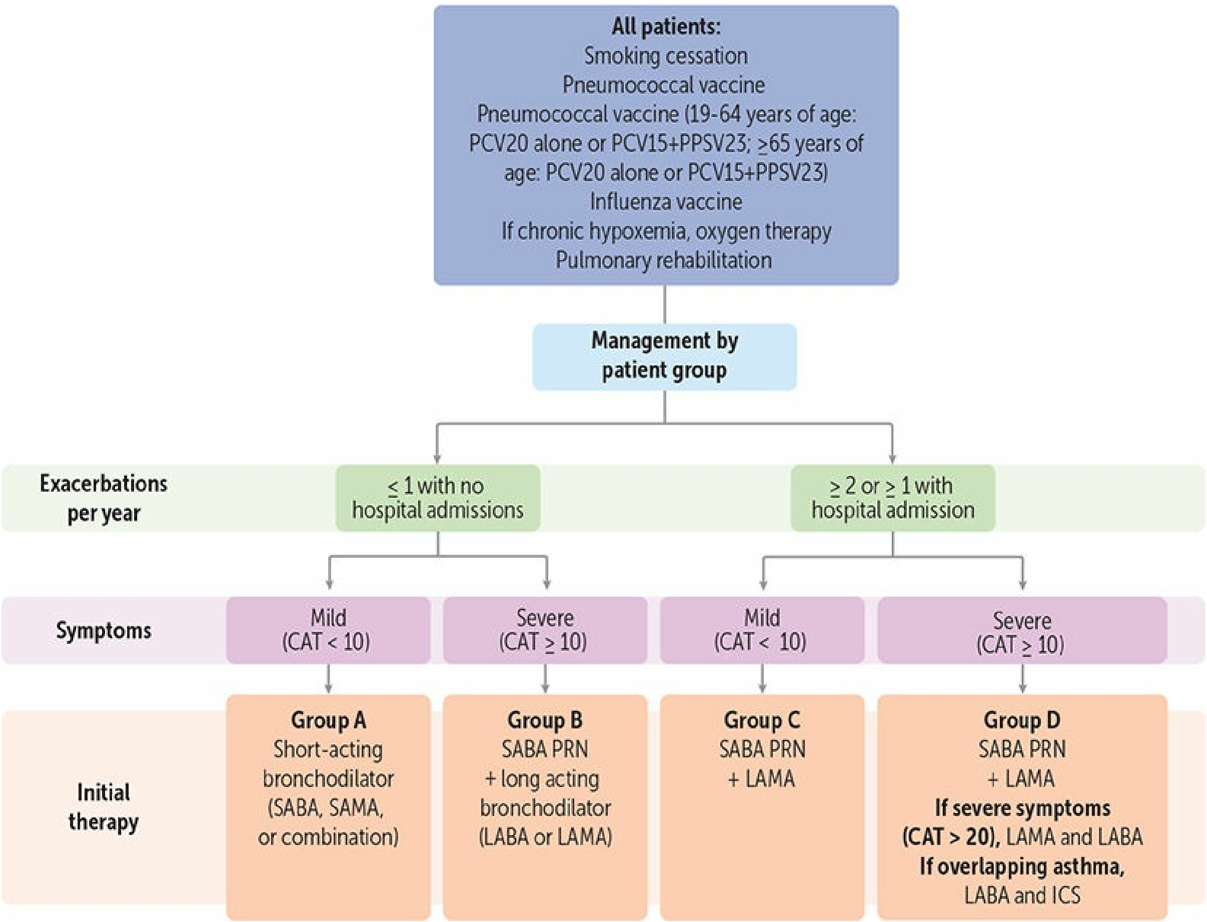

All patients:
Smoking cessation
Pneumococcal vaccine
Pneumococcal vaccine (19-64 years of age: PCV20 alone or PCV15+PPSV23; ≥65 years of age: PCV20 alone or PCV15+PPSV23)
Influenza vaccine
If chronic hypoxemia, oxygen therapy
Pulmonary rehabilitation
Management by patient group
Exacerbations per year
≤ 1 with no hospital admissions
≥ 2 or ≥ 1 with hospital admission
Symptoms
Mild (CAT < 10)
Severe (CAT ≥ 10)
Mild (CAT < 10)
Severe (CAT ≥ 10)
Initial therapy
Group A Short-acting bronchodilator (SABA, SAMA, or combination)
Group B SABA PRN + long acting bronchodilator (LABA or LAMA)
Group C SABA PRN + LAMA
Group D SABA PRN + LAMA **If severe symptoms (CAT > 20)**, LAMA and LABA **If overlapping asthma,** LABA and ICS

FIGURE 2.14-5. **Initial COPD treatment based on severity assessed using COPD assessment test (CAT).** (Reproduced with permission from USMLE-Rx.com.)

MNEMONIC

Treatment for COPD—

COPD

Corticosteroids
Oxygen (if resting SpO_2 <88% or <89% with cor pulmonale)
Prevention (smoking cessation, pneumococcal and influenza vaccines)
Dilators (β_2-agonists, anticholinergics)

RESTRICTIVE LUNG DISEASE

Characterized by a loss of lung compliance, restrictive lung diseases result in ↑ lung stiffness and ↓ lung expansion. Table 2.14-1 and Figure 2.14-2 contrast obstructive with restrictive lung disease. The etiologies of restrictive lung disease are shown in the **AIN'T** mnemonic**.**

INTERSTITIAL LUNG DISEASE

MNEMONIC

Etiology of restrictive lung disease—

If the lungs AIN’T compliant

Alveolar (edema, hemorrhage, pus)

Interstitial lung disease (idiopathic pulmonary fibrosis, usual insterstitial pneumonia, nonspecific interstitial pneumonia, chronic hypersensitivity pneumonitis, sarcoidosis with interstitial pneumonia)

Neuromuscular (myasthenia, phrenic nerve palsy, myopathy)

Thoracic wall (kyphoscoliosis, obesity, ascites, pregnancy, ankylosing spondylitis)

A heterogeneous group of disorders characterized by inflammation and/or fibrosis of the interstitium. In advanced disease, cystic spaces can develop in the lung periphery, a development that leads to the characteristic “honeycomb” pattern seen on CT (see Fig. 2.14-6A). Interstitial lung disease (ILD) is also called diffuse parenchymal lung disease (DPLD).

Subgroups of ILD:

- **Exposure related:** Asbestosis, silicosis, berylliosis, coal worker’s pneumoconiosis, medications (eg, amiodarone, bleomycin), hypersensitivity pneumonitis, radiation-induced injury
- **ILD associated with systemic disease or connective tissue diseases:** Polymyositis/dermatomyositis, sarcoidosis, amyloidosis, vasculitis, scleroderma (CREST syndrome)
- **Idiopathic:** Idiopathic pulmonary fibrosis (IPF), cryptogenic organizing pneumonia, acute interstitial pneumonia

KEY FACT

Medications and interventions that can cause or contribute to ILD include amiodarone, busulfan, nitrofurantoin, bleomycin, methotrexate, radiation, and long-term high O_2 concentration (eg, ventilators).

History/PE

- Presents with shallow**,** rapid breathing; progressive dyspnea with exertion; and a chronic nonproductive cough
- May have cyanosis, inspiratory squeaks, fine or “Velcro-like” crackles, clubbing, or right heart failure

Diagnosis

- **Best initial test:** CXR; reticular, nodular, or ground-glass pattern
- **Next best step:** If CXR is suspicious for ILD, then high-resolution CT; CT shows “honeycomb” pattern in severe disease
- **PFTs**: Restrictive pattern. Normal/↑ FEV_1/FVC, ↓ FVC, ↓ FEV_1, ↓ TLC, ↓ FVC, ↓ DLCO
- If systemic disease is suspected as the cause, the physician can consider serologic testing (eg, ANA, anti–cyclic citrullinated peptide [anti-CCP], creatine kinase [CK], aldolase, anti-Jo1, antineutrophil cytoplasmic antibody [ANCA], antitopoisomerase, anti–double-

stranded [ds]DNA).

- **Most accurate test:** Surgical biopsy. This is not recommended if CT findings are characteristic (see Fig. 2.14-6A). In IPF and rheumatologic disease, a surgical biopsy is only performed when the diagnosis is uncertain.

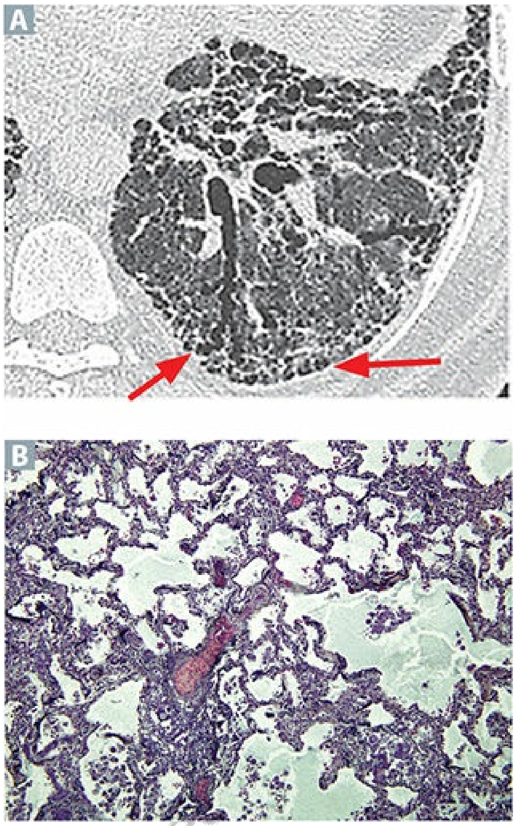


FIGURE 2.14-6. **Idiopathic pulmonary fibrosis. (A)** Chest CT showing the characteristic "honeycomb" lung that is seen in advanced disease. **(B)** Lung biopsy specimen demonstrating increased interstitial fibrosis and nonspecific inflammation with alveolar thickening. (Image A reproduced with permission from Walsh SLF, Wells AU, Sverzellati N, et al. Relationship between fibroblastic foci profusion and high-resolution CT morphology in fibrotic lung disease. *BMC Med.* 2015;13:241. Image B reproduced with permission from USMLE-Rx.com.)

Treatment

- **Supportive:** Avoidance of exposure to causative agents
- **Medications:** Anti-inflammatory/immunosuppressive agents for some disease (eg, corticosteroids), antifibrotic agents (pirfenidone, nintedanib) for IPF
- **Surgery:** Referral for lung transplantation indicated at late stages of IPF

CRYPTOGENIC ORGANIZING PNEUMONIA

Cryptogenic organizing pneumonia is a form of diffuse ILD. "Cryptogenic" refers to the idiopathic nature of the condition. "Organizing pneumonia" refers to the typical pathologic appearance of the condition wherein buds of granulation tissue form in distal air spaces (alveoli and bronchiolar lumen [bronchiolitis obliterans]). These findings are not specific to a disease, but just a type of inflammatory process.

History/PE

Typically presents with subacute fever, dry cough, shortness of breath, weight loss, anorexia, and malaise that have failed to respond to antibiotic therapy.

Diagnosis

- Other causes such as infection or autoimmune disease must be excluded.
- Radiographic findings on CXR or CT include bilateral, peripheral patchy opacities that may migrate.
- PFTs show a restrictive defect with diffusion impairment.
- Pathologic examination of biopsy specimens is diagnostic (generally surgical biopsy is required, although transbronchial biopsy can be attempted).

Treatment

Treatment with corticosteroids results in dramatic clinical and radiologic response. Relapse is common on tapering steroids. Overall, prognosis is excellent.

SYSTEMIC SARCOIDOSIS

A multisystem disease of unknown etiology characterized by infiltration of noncaseating granulomas. In the United States, more commonly found in females (although it occurs in males too) of African or Northern European descent. Most often arises in the third or fourth decade of life.

History/PE

- Systemic sarcoidosis can present with fever, cough, dyspnea, malaise, weight loss, or arthritis.
- **Lofgren syndrome:** Erythema nodosum, bilateral hilar adenopathy, migratory polyarthralgia, and fever; associated with good prognosis

Q

A 25-year-old Black woman presents to the physician’s office with painful bumps on her shins, weight loss, and cough. Examination reveals a prominent 1-cm right axillary lymph node. What is the next best step for diagnosis?

- Extrapulmonary manifestations can involve the following organs: liver, eyes (uveitis), skin (erythema nodosum, violaceous skin plaques), central nervous system (CNS), heart (third-degree heart block, arrhythmias), and kidneys.

Diagnosis

- **Best initial test:** CXR shows bilateral hilar adenopathy and reticular opacities (upper lobe predominant). Figure 2.14-7 illustrates CXR findings of sarcoidosis. High-resolution CT is usually done following suspicious CXR.

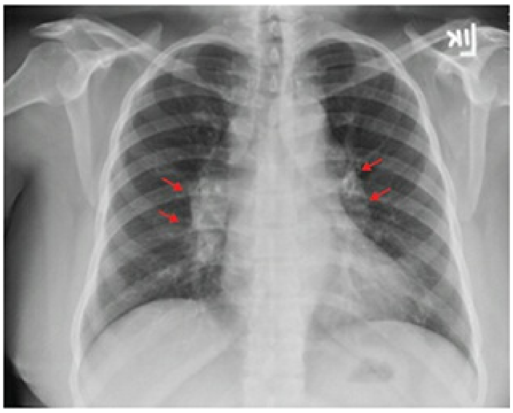


FIGURE 2.14-7. **Bilateral hilar lymphadenopathy *(arrows)* in a patient with pulmonary sarcoidosis.** (Reproduced with permission from USMLE-Rx.com.)

- **Next best step:** If CXR/CT is suspicious, then bronchoscopic biopsy. Noncaseating granulomas are diagnostic in the presence of a compatible clinical picture with exclusion of other diseases.
- **PFTs:** Restrictive pattern and ↓ DLCO.

MNEMONIC

***Learning the features of sarcoid can be* GRUELING—**

Granulomas
a**R**thritis
Uveitis
Erythema nodosum
Lymphadenopathy (particularly hilar, seen on CXR)
Interstitial fibrosis
Negative tuberculosis (TB) test
Gammaglobulinemia

- **Other findings:** ↑ serum angiotensin-converting enzyme (ACE) levels (neither sensitive nor specific), hypercalcemia, hypercalciuria, ↑ alkaline phosphatase (with liver involvement), lymphopenia, cranial nerve defects, arrhythmias.

Treatment

- **Asymptomatic:** Observation
- **Symptomatic:** Systemic corticosteroids indicated for deteriorating respiratory function, constitutional symptoms, hypercalcemia, and extrathoracic organ involvement
- **Refractory disease:** Immunosuppressants (eg, methotrexate, azathioprine, tumor necrosis factor [TNF]-α inhibitors)
- **Lofgren syndrome:** NSAIDs and supportive therapy

KEY FACT

Lofgren syndrome is a type of sarcoidosis with the following triad: arthritis, erythema nodosum, and bilateral hilar adenopathy. Associated with a good prognosis.

HYPERSENSITIVITY PNEUMONITIS

Alveolar thickening and noncaseating granulomas secondary to environmental exposure (eg, farmer's lung seen in farmers and cattle workers due to chronic inhalation of mold that grows on hay and grain or pigeon breeder's disease due to chronic inhalation of particles from feathers or bird droppings)

History/PE

- **Acute:** Dyspnea, fever, malaise, shivering, and cough starting 4 to 6 hours after exposure; the physician should gather a job/travel history to determine exposure
- **Chronic:** Presents with progressive dyspnea; physical examination reveals fine bilateral rales

Diagnosis

Appearance on CXR/CT is variable, but upper lobe fibrosis is a common feature of chronic disease.

Treatment

The patient should avoid ongoing exposure to inciting agents; the physician should prescribe corticosteroids to ↓ chronic inflammation.

A

This is presumed sarcoidosis. Biopsy of the right axillary lymph node is the next best step for diagnosis and is less invasive than transbronchial lung biopsy.

PNEUMOCONIOSIS

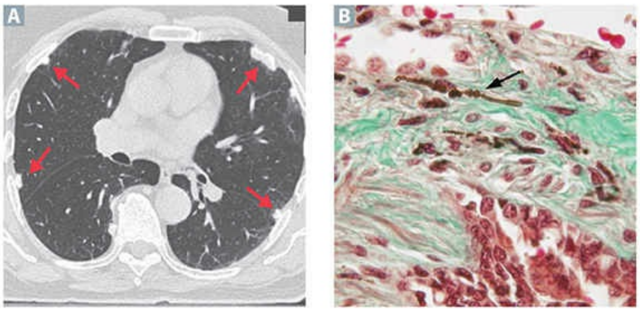
Pneumoconiosis refers to lung conditions caused by the inhalation of organic or nonorganic airborne dust and fibers. Risk factors include prolonged occupational exposure and inhalation of small inorganic dust particles.

History/PE/Diagnosis

Table 2.14-6 outlines the findings and diagnostic criteria associated with common pneumoconioses.

TABLE 2.14-6. **Diagnoses of Pneumoconioses**

DISORDER	HISTORY	IMAGING FINDINGS[a]	COMPLICATIONS
Asbestosis	Work involving the manufacture of tile or brake linings, insulation, construction, demolition, or shipbuilding Presents 15–20 years after initial exposure	Linear opacities at lung bases and interstitial fibrosis; calcified pleural plaques (Image A) indicative of benign pleural disease; Image B shows ferruginous bodies in alveolar septum	↑ risk for mesothelioma (rare) and lung cancer; the risk for lung cancer is higher in smokers; the most common malignancy associated with asbestos exposure is bronchogenic carcinoma
Coal workers' disease	Work in underground coal mines	Small nodular opacities (<1 cm) in upper lung zones	Progressive massive fibrosis
Silicosis	Work in mines or quarries or with glass, pottery, or silica	Small (<1 cm) nodular opacities in upper lung zones; eggshell calcifications	↑ risk for TB; need annual TB test Progressive massive fibrosis
Berylliosis	Work in high-technology fields such as aerospace, nuclear, and electronics plants; ceramics industries; foundries; plating facilities; dental material sites; or dye manufacturing	Diffuse infiltrates; hilar adenopathy	Requires chronic corticosteroid treatment



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[a] Spirometry, consistent with restrictive disease.

Image A reproduced with permission from Miles SE, Sandrini A, Johnson AR, et al. Clinical consequences of asbestos-related diffuse pleural thickening: a review. *J Occup Med Toxicol* 2008;3:20. Image B reproduced with permission from Mizell KN, Morris CG, Carter JE. Antemortem diagnosis of asbestosis by screening chest radiograph correlated with postmortem histologic features of asbestosis: a study of 273 cases. *J Occup Med Toxicol.* 2009 Jun 12;4:14. doi: 10.1186/1745-6673-4-14.

Treatment

Avoidance of triggers; supportive therapy and supplemental O_2.

EOSINOPHILIC PULMONARY SYNDROMES

A diverse group of disorders characterized by eosinophilic pulmonary infiltrates and abnormal peripheral blood eosinophilia. Includes ABPA, Loffler syndrome, acute and chronic eosinophilic pneumonia, eosinophilic granulomatosis polyangitis, and drug-induced disorders (eg, NSAIDs, nitrofurantoin, sulfonamides).

History/PE

Presents with dyspnea, cough, potentially blood-tinged sputum, and/or fever.

Diagnosis

- **Complete blood cell count (CBC):** May reveal peripheral eosinophilia (≥500 eosinophils/uL)
- **CXR:** Shows pulmonary infiltrates
- **Bronchoalveolar lavage:** ↑ eosinophils (>25%)

KEY FACT

Loffler syndrome is a form of eosinophilic pulmonary disease characterized by absent or mild respiratory symptoms (most often dry cough), fleeting migratory pulmonary opacities, and peripheral blood eosinophilia.

Treatment

Removal of the extrinsic cause or treatment of underlying infection (eg, helminths) if identified. Corticosteroid treatment may be used.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

ABPA is a hypersensitivity reaction of airways to colonization by *Aspergillus*. As a result of recurrent inflammation, obstruction, and mucous secretions, bronchiectasis and fibrosis develop. Early treatment may prevent progression to bronchiectasis or pulmonary fibrosis.

History/PE

Patients often have underlying asthma or CF, and they present with recurrent fever, bronchial obstruction, brownish expectoration, and hemoptysis.

Diagnosis

- Initial tests look for evidence of *Aspergillus* sensitization (eg, *Aspergillus*-specific IgE antibodies or positive *Aspergillus* skin prick test). Negative results rule out aspergillosis.
- Patients sensitized to *Aspergillus* should undergo further laboratory testing for total serum IgE, *Aspergillus* precipitins, and eosinophil counts (generally >500 cells/uL).
- Sputum may have eosinophil-rich plugs and Charcot-Leyden crystals. Culture of sputum may grow *Aspergillus*.
- Imaging with CT of chest or a CXR may show evidence of bronchiectasis.

Treatment

- Systemic glucocorticoids (prednisone) and antifungal therapy (itraconazole or voriconazole) may be used.
- Optimization of asthma treatment with possible addition of biologic agents (eg, omalizumab). Patients with CF may also benefit from omalizumab.
- Patients should reduce *Aspergillus* exposure at home or work.

Complications

Complications include acute/chronic invasive pulmonary aspergillosis and aspergilloma.

ACUTE RESPIRATORY FAILURE

HYPOXEMIA

Hypoxemia is a below normal arterial oxygen level, normally defined as PaO_2 <60 mm Hg. Causes include ventilation-perfusion (V/Q) mismatch, right-to-left shunt, hypoventilation, low inspired O_2 content (high altitudes), and diffusion impairment.

History/PE

Findings depend on the etiology. ↓ saturation of peripheral oxygen (SpO_2), cyanosis, tachypnea, shortness of breath, pleuritic chest pain (caused by wheezing, coughing), and altered mental status may be seen.

Diagnosis

- **Best initial test:** ABGs; exhibition of ↓ PaO_2. Calculate the alveolar-arterial (A-a) oxygen gradient:$150 - (\text{PaCO}_2/0.8) - \text{PaO}_2$. (Note: Presumes P_{atm} is 760 mm Hg at sea level, fraction of inspired oxygen [FiO_2] is 0.21).
- **CXR:** To evaluate for an infiltrative process (eg, pneumonia), atelectasis, a large pleural effusion, or pneumothorax and to assess for acute respiratory distress syndrome (ARDS). An ↑ A-a gradient suggests shunt, V/Q mismatch, or diffusion impairment. Figure 2.14-8 summarizes the approach toward patients who have hypoxemia.

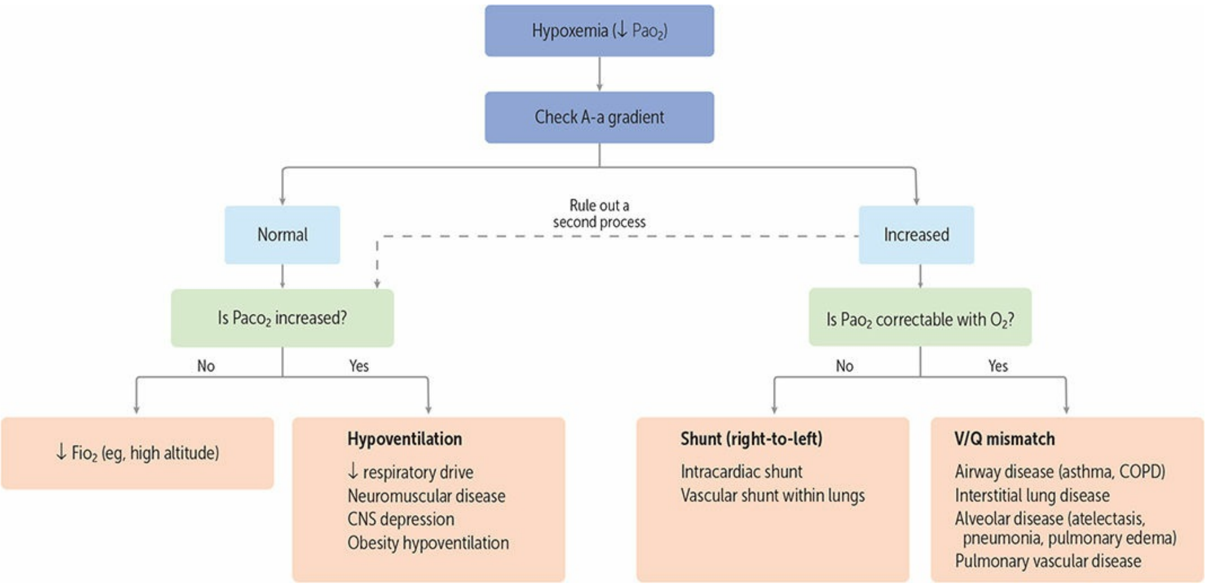

Hypoxemia (↓ PaO_2)
Check A-a gradient
Normal
Rule out a second process
Increased
Is PaCO_2 increased?
Is PaO_2 correctable with O_2?
No
Yes
No
Yes
↓ FiO_2 (eg, high altitude)
Hypoventilation
↓ respiratory drive
Neuromuscular disease
CNS depression
Obesity hypoventilation
Shunt (right-to-left)
Intracardiac shunt
Vascular shunt within lungs
V/Q mismatch
Airway disease (asthma, COPD)
Interstitial lung disease
Alveolar disease (atelectasis, pneumonia, pulmonary edema)
Pulmonary vascular disease

FIGURE 2.14-8. **Determination of the mechanism of hypoxemia.** (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

If the problem is hypoventilation or low inspired oxygen, the A-a gradient will be normal. If the problem is ventilation/perfusion (V/Q) mismatch or shunting, the A-a gradient will increase.

Treatment

- Address the underlying etiology.
- Administer O_2 before initiating evaluation.
- ↑ oxygenation parameters if the patient is on mechanical ventilation (see Table 2.14-7).

TABLE 2.14-7. **Mechanical Ventilator Parameters Affecting Oxygenation and Ventilation**

↑ OXYGENATION	↑ VENTILATION
↑ Fio_2	↑ RR
↑ Positive end-expiratory pressure (PEEP)	↑ VT

- In hypercapnic patients**,** ↑ ventilation (↑ respiratory rate [RR] or ↑ VT) to ↑ CO_2 exchange.

ACUTE RESPIRATORY DISTRESS SYNDROME

- Respiratory failure with refractory hypoxemia, ↓ lung compliance, and noncardiogenic pulmonary edema with a $PaO_2/FiO_2 \leq 300$. Pathogenesis is thought to be dependent on endothelial injury.
- Common triggers are as follows: Sepsis (most common), severe pulmonary infection (pneumonias), aspiration, blood transfusions, inhaled/ingested toxins, drowning, and trauma.
- Overall mortality is 30% to 40%.

History/PE

- Presents with acute-onset (12–48 hours) tachypnea, dyspnea, and tachycardia ± fever, cyanosis, labored breathing, diffuse high-pitched rales, and hypoxemia in the setting of one of the systemic inflammatory causes or exposure.
- Additional findings are as follows:
  - **Phase 1 (acute injury):** Normal physical examination; possible respiratory alkalosis
  - **Phase 2 (6–48 hours):** Hyperventilation, hypocapnia, widening A-a gradient
  - **Phase 3:** Acute respiratory failure, tachypnea, dyspnea, ↓ lung compliance, scattered rales, diffuse chest opacities on CXR (see Fig. 2.14-9)

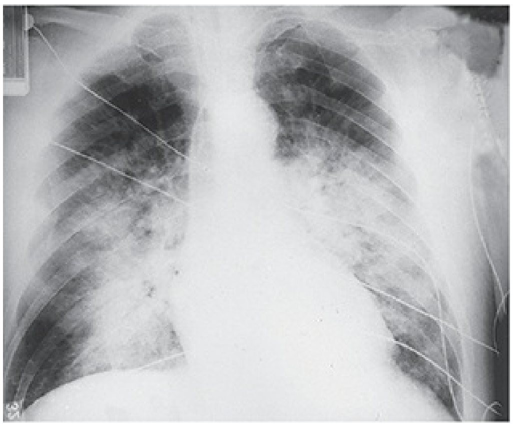


FIGURE 2.14-9. **Anteroposterior CXR showing a diffuse alveolar filling pattern secondary to ARDS.** (Reproduced with permission from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York, NY: McGraw-Hill; 2005.)

  - **Phase 4:** Severe hypoxemia unresponsive to therapy; ↑ intrapulmonary shunting; metabolic and respiratory acidosis

Diagnosis

The criteria for an ARDS diagnosis (according to the Berlin definition) are as follows:

- Acute onset (<1 week) of respiratory distress.
- **CXR:** Bilateral alveolar opacities consistent with pulmonary edema. Pulmonary edema on CXR <24 hours after trauma may suggest pulmonary contusion instead of ARDS; features of pulmonary contusions are shown in Figure 2.14-10.

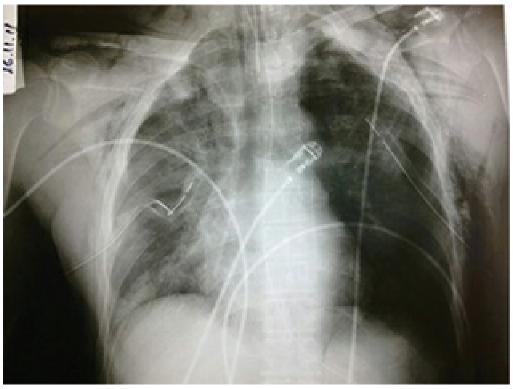


FIGURE 2.14-10. **Pulmonary contusion.** Rib fractures, subcutaneous emphysema, and lung opacities on right corresponding to lung contusion. Pneumothorax of left lung. (Reproduced with permission from Sertaridou E, Papaioannou V, Kouliatsis G, et al. Traumatic asphyxia due to blunt chest trauma: a case report and literature review. *J Med Case Rep*. 2012;6:257 doi:10.1186/1752-1947-6-257.)

- A Pao_2/Fio_2 ratio ≤300 with positive end-expiratory pressure (PEEP)/continuous positive airway pressure (CPAP) ≥5 cm H_2O.
- Respiratory failure not completely explained by heart failure.

Treatment

- Treat the underlying disease and maintain adequate perfusion to prevent end-organ damage.
- Prone positioning in select patients with severe ARDS (eg, severe ARDS with Pao_2/Fio_2 ratio <150 mm Hg and Fio_2 ≥0.6 and PEEP ≥5 cm H_2O) reduces mortality.
- Use mechanical ventilation with low tidal volumes (6 cc/kg of ideal body weight) to minimize ventilator-induced lung injury by overdistention of alveoli.
- Use PEEP to recruit collapsed alveoli and titrate PEEP and Fio_2 to achieve adequate oxygenation.
  - To ↑ Pao_2, ↑ PEEP.
  - Keep Fio_2 ≤60% (0.6), if possible, to prevent oxygen toxicity.
- Goal oxygenation is Pao_2 >55 mm Hg or Spo_2 >88%.
- Extubation may be attempted if:
  - The cause of respiratory failure has improved.
  - Ventilator support required is minimal (low PEEP, low pressure support).
  - Oxygen supplementation is easily accomplished without the support of PEEP or other adjuvant treatments.
  - Patient passes a spontaneous breathing trial.

MECHANICAL VENTILATION

Mechanical ventilation is the process by which gas is moved to and from the lungs by an external device to artificially support their functions. It may be invasive (via tracheostomy, endotracheal tube) or noninvasive (via mask).

Indications For Invasive Mechanical Ventilation

Indications for mechanical ventilation include but are not limited to:

- Inadequate oxygenation (acute hypoxemia, eg, atelectasis, small airway/parenchymal disease)
- Inadequate ventilation (acute hypercapnia, eg, flail chest or inadequate ventilation)
- Inability to maintain airway (eg, trauma, intoxication, postictal state)
- Hemodynamic instability

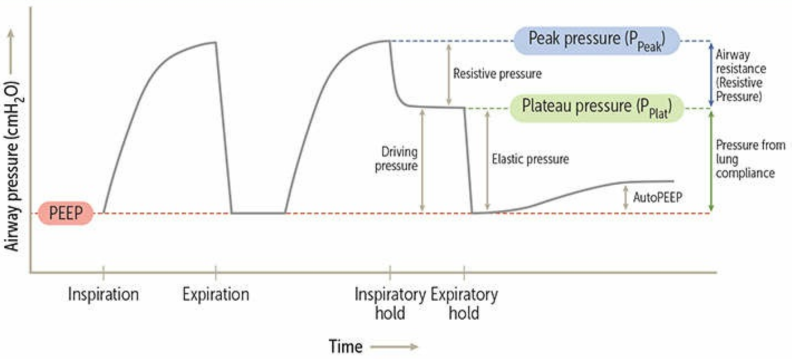
KEY FACT

In flail chest, multiple rib fractures result in a floppy segment that moves paradoxically due to negative intrathoracic pressure on inspiration. By increasing positive intrathoracic pressure, positive-pressure ventilation improves oxygenation and causes the flail segment to move normally.

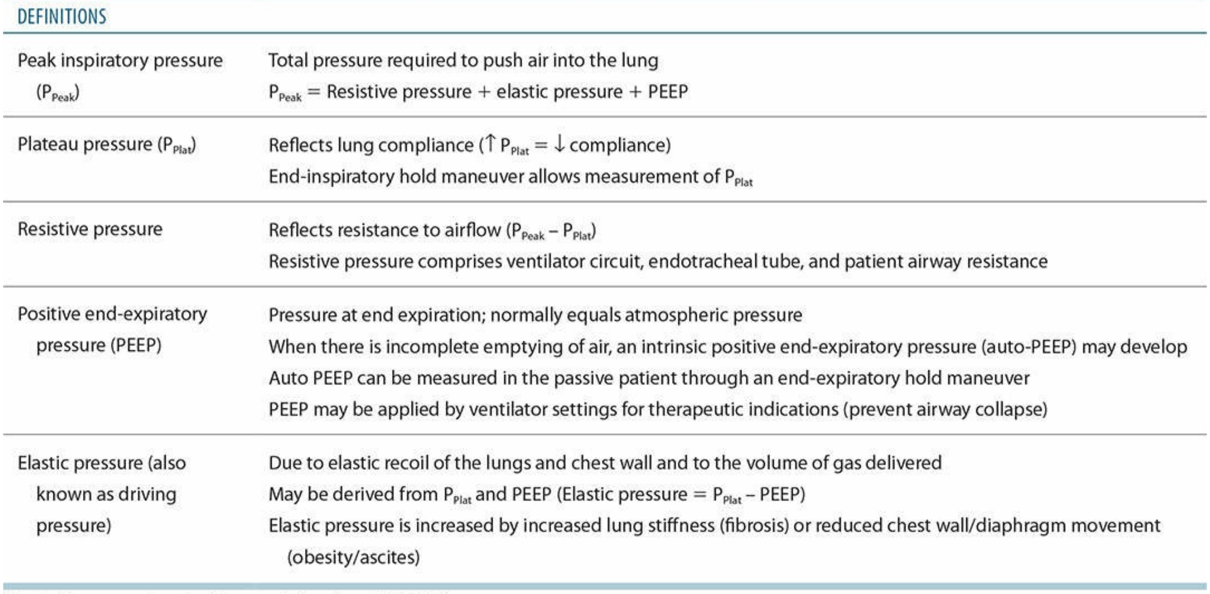
Ventilator Mechanics

Table 2.14-8 depicts changes in lung pressures during ventilation. Table 2.14-9 shows abnormal ventilator waveforms and explains the significance.

TABLE 2.14-8. Respiratory Mechanics


Airway pressure (cmH_2O)
PEEP
Peak pressure (P_{Peak})
Resistive pressure
Plateau pressure (P_{Plat})
Airway resistance (Resistive Pressure)
Driving pressure
Elastic pressure
Pressure from lung compliance
AutoPEEP
Inspiration
Expiration
Inspiratory hold
Expiratory hold
Time

AIRWAY PRESSURE/TIME CURVE

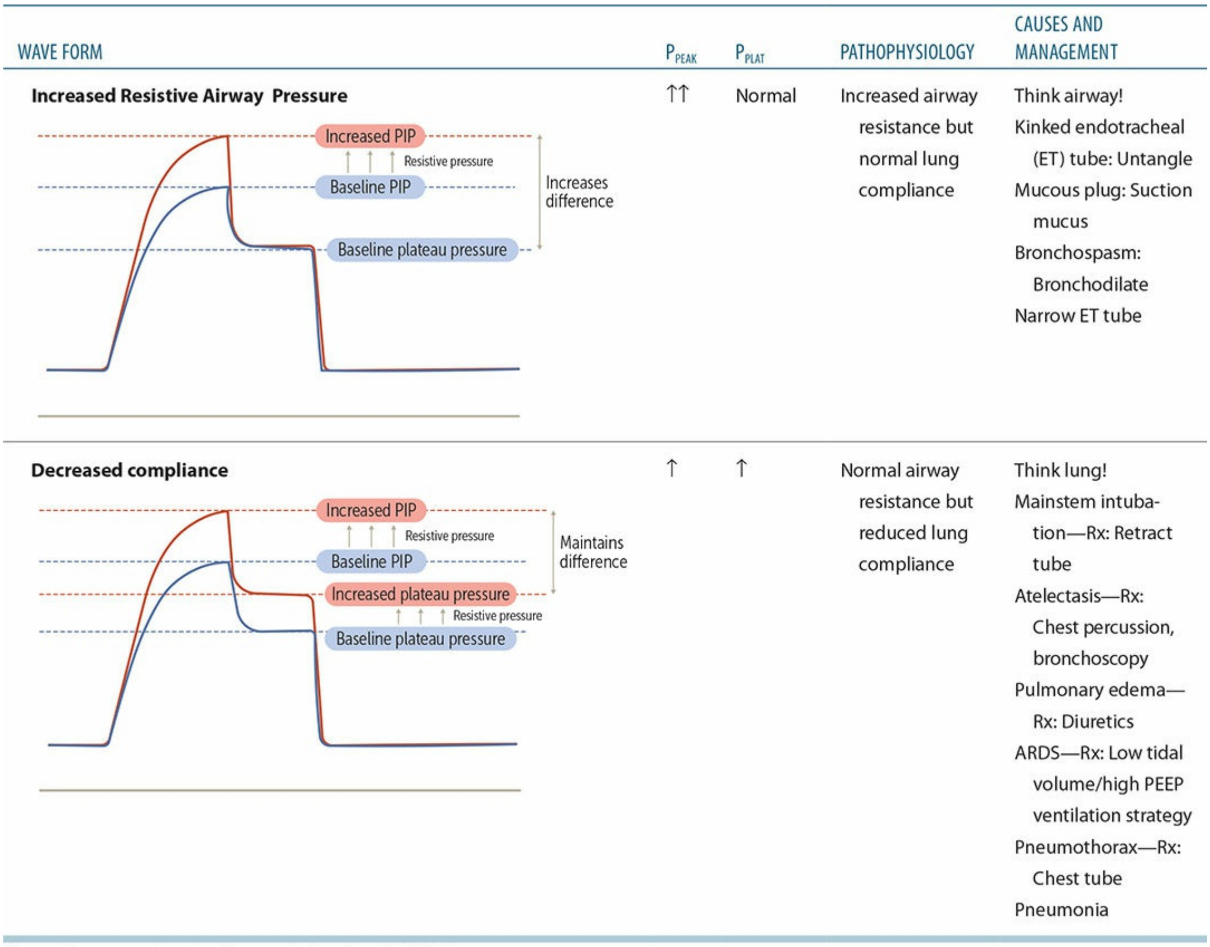


DEFINITIONS

Peak inspiratory pressure (P_{Peak})	Total pressure required to push air into the lung P_{Peak} = Resistive pressure + elastic pressure + PEEP
Plateau pressure (P_{Plat})	Reflects lung compliance (↑ P_{Plat} = ↓ compliance) End-inspiratory hold maneuver allows measurement of P_{Plat}
Resistive pressure	Reflects resistance to airflow ($P_{Peak} - P_{Plat}$) Resistive pressure comprises ventilator circuit, endotracheal tube, and patient airway resistance
Positive end-expiratory pressure (PEEP)	Pressure at end expiration; normally equals atmospheric pressure When there is incomplete emptying of air, an intrinsic positive end-expiratory pressure (auto-PEEP) may develop Auto PEEP can be measured in the passive patient through an end-expiratory hold maneuver PEEP may be applied by ventilator settings for therapeutic indications (prevent airway collapse)
Elastic pressure (also known as driving pressure)	Due to elastic recoil of the lungs and chest wall and to the volume of gas delivered May be derived from P_{Plat} and PEEP (Elastic pressure = P_{Plat} – PEEP) Elastic pressure is increased by increased lung stiffness (fibrosis) or reduced chest wall/diaphragm movement (obesity/ascites)

Illustration reproduced with permission from USMLE-Rx.com.

TABLE 2.14-9. Pathologic Waveforms During Ventilation


Increased PIP
Resistive pressure
Baseline PIP
Increases difference
Baseline plateau pressure
Increased PIP
Resistive pressure
Baseline PIP
Maintains difference
Increased plateau pressure
Resistive pressure
Baseline plateau pressure

WAVE FORM	P_{PEAK}	P_{PLAT}	PATHOPHYSIOLOGY	CAUSES AND MANAGEMENT
Increased Resistive Airway Pressure	↑↑	Normal	Increased airway resistance but normal lung compliance	Think airway! Kinked endotracheal (ET) tube: Untangle Mucous plug: Suction mucus Bronchospasm: Bronchodilate Narrow ET tube
Decreased compliance	↑	↑	Normal airway resistance but reduced lung compliance	Think lung! Mainstem intubation—Rx: Retract tube Atelectasis—Rx: Chest percussion, bronchoscopy Pulmonary edema—Rx: Diuretics ARDS—Rx: Low tidal volume/high PEEP ventilation strategy Pneumothorax—Rx: Chest tube Pneumonia

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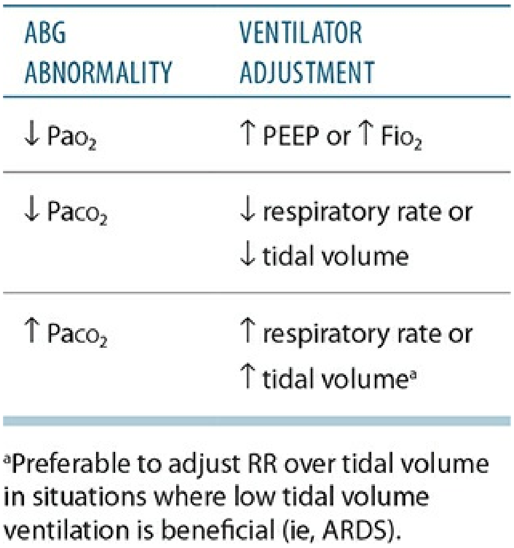
Ventilator Settings

Key initial settings for volume assist/control follow:

- Tidal volume is set at 6 to 8 mL/kg in obstructive lung disease (eg, chronic obstructive pulmonary disease [COPD]) or 6 mL/kg in ARDS (ie, restrictive disease).
- The rate is generally set lower for obstructive diseases as opposed to ARDS (eg, 10–14/min in obstructive lung disease and 14–18/min in ARDS; however, specific settings vary based on disease process and ABG).
- Fio_2 is initially started at 100% and titrated down to maintain arterial oxygen saturation (SaO_2) of 88% to 95% or Pao_2 55 to 80 mm Hg. Ideally, FiO_2 is reduced to ≤60% to prevent oxygen toxicity.
- Use ARDSnet PEEP/FiO2 table for guidnace on PEEP for ARDS management. This is to prevent barotrauma. For obstructive disease, start with PEEP of 0 to 5 cm H_2O.
- **I:E ratio:** In obstructive lung disease, the inspiratory-to-expiratory time ratio is higher (I:E >1:3) than with ARDS (I:E > 1:1.5). This is needed because the lungs take more time to effectively empty due to obstructed airways.
- After initiation of ventilation, changes in settings should be based on ABGs. Refer to Table 2.14-10.

TABLE 2.14-10. Ventilator Setting Adjustments Based on ABG Abnormalities



ABG ABNORMALITY	VENTILATOR ADJUSTMENT
↓ Pao_2	↑ PEEP or ↑ Fio_2
↓ Paco_2	↓ respiratory rate or ↓ tidal volume
↑ Paco_2	↑ respiratory rate or ↑ tidal volume[a]

[a] Preferable to adjust RR over tidal volume in situations where low tidal volume ventilation is beneficial (ie, ARDS).

Complications of Mechanical Ventilation

Ventilation is associated with multiple complications, including ventilator-associated lung injury and hypotension.

Ventilator-Induced Lung Injury

Acute lung injury inflicted by mechanical ventilation that may result in increased mortality and morbidity. Some mechanisms are described next:

- **Volutrauma:** Caused by excessive stretch by high tidal volume. This can be prevented by using lower tidal volumes.
- **Barotrauma:** Due to high pressures. In ARDS, a lung-protective strategy (plateau pressure <30 cmH_2O) minimizes barotrauma.
- **Atelectrauma:** Due to cyclical opening and closing of alveoli. This can be minimized with ↑ PEEP.
- **Biotrauma:** Due to inflammatory mediators possibly caused by other forms of trauma.
- **Oxygen effect:** Possibility for high Fio_2 to cause lung damage. This is less likely at Fio_2 <0.6.

KEY FACT

In left heart failure, PEEP is beneficial, as ↑ intrathoracic pressure causes ↓ preload and ↓ afterload. On the other hand, ↑ PEEP worsens right heart failure (↑ increased intrathoracic and ↑ pulmonary vascular pressures).

KEY FACT

For acute brain injury (stroke) target an Spo_2 of 94% to 98% or a Pao_2 of 80 to 100 mm Hg to help the brain oxygenate. Both very high PEEP and hypoxemia can increase intracranial pressure (ICP) and cause cerebral ischemia.

Acute Hypotension

- **Tension pneumothorax:** Acute hypotension with tachycardia and sudden increase in peak inspiratory pressure is suggestive of tension pneumothorax. CXR should be ordered.

- **Decreased venous return:** High levels of PEEP cause increased intrathoracic pressure and decreased venous return. This may cause or exacerbate hypotension.
- Sedatives and opioids used in ventilated patients may cause hypotension.

CORONAVIRUSES AND COVID-19

RNA viruses that can infect animals and humans. Global outbreaks of severe disease have been caused by coronaviruses, including the severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak of 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak of 2012. SARS-CoV-2 emerged in December 2019, and this led to the COVID-19 pandemic. The first cases were reported in Wuhan, China. A detailed discussion of COVID-19 follows.

Pathogenesis

The pathogenesis of COVID-19 involves an exaggerated inflammatory response to viral infection (cytokine storm syndrome [CSS]). CSS may result in fever, multiorgan dysfunction, cardiac and renal injury, and ARDS.

Q

A 25-year-old man in the intensive care unit (ICU) is intubated, following an acute asthma exacerbation. A repeat ABG is sent after intubation and shows a pH of 7.5, a $Pa\text{CO}_2$ of 33 mm Hg, and an HCO_3^- of 26 mEq/L. What adjustments, if any, should the physician make to the ventilator settings?

History/PE

- The virus is spread by respiratory droplets and has an incubation period of 2 to 14 days (average of 5 days).
- Clinical presentation ranges from asymptomatic or mildly symptomatic to severe and life-threatening disease.
- Patients with mild infection may present with fever and upper respiratory tract symptoms such as cough, sore throat, and nasal congestion. Anosmia and ageusia (loss of smell and taste, respectively) are common. Additionally, GI symptoms, such as nausea, vomiting, and diarrhea, are also reported with COVID-19.
- More serious infections may result in dyspnea, respiratory failure, ARDS, shock, or multiorgan dysfunction syndrome.
- Thromboembolic events (such as pulmonary embolism) may occur.

Diagnosis

- **Most sensitive test:** Nucleic acid amplification test ([NAAT] also known as reverse transcription quantitative polymerase chain reaction [RT-PCR]) of nasopharyngeal samples. Rapid antigen testing has lower sensitivity; however, point-of-care testing allows for immediate results and communication of advice so patients can isolate and monitor sooner.
- CXR may show bilateral opacities. CT may show multifocal, bilateral, peripheral ground-glass opacities (often affecting the posterior portion of the lower lobes), consolidation, and

air bronchograms (Fig. 2.14-11).

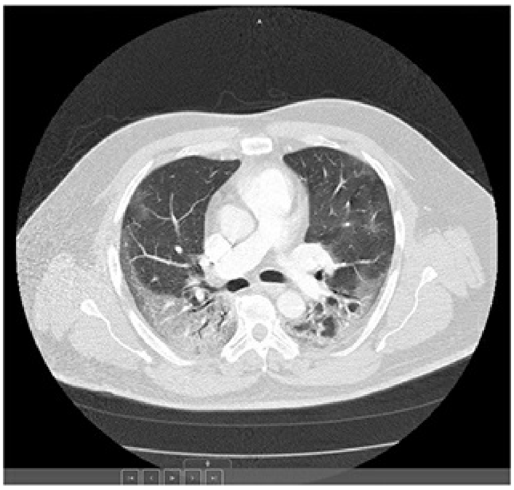


FIGURE 2.14-11. **CT angiogram of chest in COVID-19 pneumonia shows dense right lower lobe and left lower lobe opacities and air bronchograms**. (Reproduced with permission from USMLE-Rx.com, courtesy of Dr. Arjun Iyer.)

- **Laboratory findings:** Abnormal blood counts (eg, lymphopenia [most common laboratory finding], thrombocytopenia), coagulation studies (eg, ↑ D-dimer), inflammatory markers (eg, ↑ C-reactive protein [CRP]), and other biochemical tests (eg, ↑ lactate dehydrogenase [LDH], ↑ alanine aminotransferase [ALT], ↑ aspartate aminotransferase [AST], ↑ creatinine) are commonly seen in hospitalized patients.

Treatment

Mild cases can be managed at home with isolation, monitoring, and symptomatic treatment (eg, antipyretics, analgesics, antitussives, hydration). Patients with mild to moderate COVID-19 at high risk for progression to severe disease may be treated with neutralizing antibodies or antivirals. For severe cases, inpatient care is needed.

Prevention

- **Personal preventive strategies:** Social distancing (maintaining distance of 6 feet, avoiding crowds), mask wearing, handwashing, use of hand sanitizer, reducing hand-to-face contact, good ventilation.
- **Strategies by healthcare personnel:** Personal protective equipment ([PPE], gowns, gloves, eye protection) while caring for patients with COVID-19. For aerosol-generating procedures, an N95 mask must be used.
- **Vaccines:** Reduce severity of illness.

A

This patient has an uncompensated respiratory alkalosis caused by ↑ ventilation. To ↓ ventilation, tidal volume can be ↓ or respiratory rate can be slowed; however, reducing the tidal volume can trigger an ↑ in ventilatory rate, exacerbating the situation.

PULMONARY VASCULAR DISEASE

PULMONARY HYPERTENSION/COR PULMONALE

- **Pulmonary hypertension (PH):** Elevated mean pulmonary arterial pressure (>20 mm Hg) at rest
- Classified into the following groups:
  - Group 1: Pulmonary arterial hypertension (PAH)
  - Group 2: ↑ pulmonary venous pressure from left-sided heart disease
  - Group 3: Hypoxic vasoconstriction secondary to chronic lung disease
  - Group 4: Chronic thromboembolic disease
  - Group 5: Pulmonary hypertension with a multifactorial etiology
- **Core pulmonale (group 3):** Alteration in structure and function of the right ventricle (RV) of the heart caused by a primary disorder of the respiratory system. Right-sided heart failure can occur in severe cases.

History/PE

- Presents with dyspnea, syncope on exertion, fatigue, lethargy, chest pain, and/or symptoms of right-sided congestive heart failure (CHF) (edema, abdominal distention, JVD)
- ***Hx:*** COPD, ILD, heart disease, sickle cell anemia, emphysema, and pulmonary embolism
- ***PE:*** Loud, palpable S_2 (often split), a flow murmur, an S_4, or a parasternal heave; patient may also be hypoxemic, especially on exertion

KEY FACT

Other etiologies of embolic disease include postpartum status (amniotic fluid emboli), fracture (fat emboli), cardiac surgery (air emboli), and endovascular procedure (cholesterol emboli).

Diagnosis

- **Best initial test:** Echocardiogram that estimates pulmonary artery (PA) pressure and assesses RV function
- **CXR:** Shows enlargement of central pulmonary arteries with rapid tapering of the distal vessels (pruning)
- **ECG:** Demonstrates right ventricular hypertrophy (RVH)
- **Diagnostic test of choice:** Right heart catheterization; mean pulmonary artery pressure >20 mm Hg (normal: 8–20 mm Hg)

Treatment

- Treat underlying disease.
- Supportive therapy: Supplemental O_2, diuretics; some patients may also benefit from exercise therapy
- Consider digoxin and anticoagulation in patients with underlying left ventricle systolic dysfunction and atrial fibrillation
- **Group 1 (primary PAH):** Prostanoids (eg, beraprost, epoprostenol, iloprost, treprostinil), endothelin receptor antagonists (eg, ambrisentan, bosentan, and macitentan), and phosphodiesterase (PDE) inhibitors (eg, sildenafil, tadalafil, vardenafil) can be added to improve hemodynamics and increase exercise tolerance. Some patients have

vasoreactivity and respond well to calcium channel blockers

- **Group 4 (thromboembolic disease):** Surgical thromboendarterectomy; anticoagulation is recommended for everyone; balloon pulmonary angioplasty and riociguat are the alternatives for chronic thromboembolic pulmonary hypertension (CTEPH)

PULMONARY THROMBOEMBOLISM

An occlusion of the pulmonary vasculature by a blood clot. Ninety-five percent of emboli originate from deep venous thrombosis (DVT) in the deep leg veins (eg, femoral vein). May lead to pulmonary infarction, right heart failure, and hypoxemia.

History/PE

- Factors predisposing to thromboembolism are summarized by the Virchow triad (see Table 2.14-11).

TABLE 2.14-11. **Virchow Triad for Venous Thrombosis**

VENOUS STASIS	ENDOTHELIAL INJURY	HYPERCOAGULABILITY
Immobility	Trauma	Pregnancy, postpartum
CHF	Surgery	Cigarette smoking
Obesity	Recent fracture	Oral contraceptive pill (OCP) use
↑ central venous pressure (eg, renal failure)	Previous DVT	Coagulation disorders (eg, protein C/ protein S deficiency, factor V Leiden)
		Malignancy
		Severe burns

MNEMONIC

Wells criteria—Consider when the history and physical exam are suggestive of DVT to assess the risk of pulmonary embolism

SHIT PMH

Symptoms of DVT: 3 points
History of DVT or PE: 1.5 points
Immobilization (≥3 days): 1.5 points
Tachycardia (HR >100/min): 1.5 points
Postop (surgery within previous 4 weeks): 1.5 points
Malignancy: 1 point
Hemoptysis: 1 point
Total point value = 11

- Presents with sudden-onset or subacute dyspnea, pleuritic chest pain, low-grade fever, cough, tachypnea, tachycardia, and rarely, hemoptysis (indicates pulmonary infarction).
- May have history of immobility (eg, long plane ride, bedbound)
- Examination that may reveal a loud P_2 and prominent jugular A waves with right heart

failure.
- Acute massive pulmonary embolism: Presents with hypotension, JVD, and new-onset right bundle branch block.

MNEMONIC

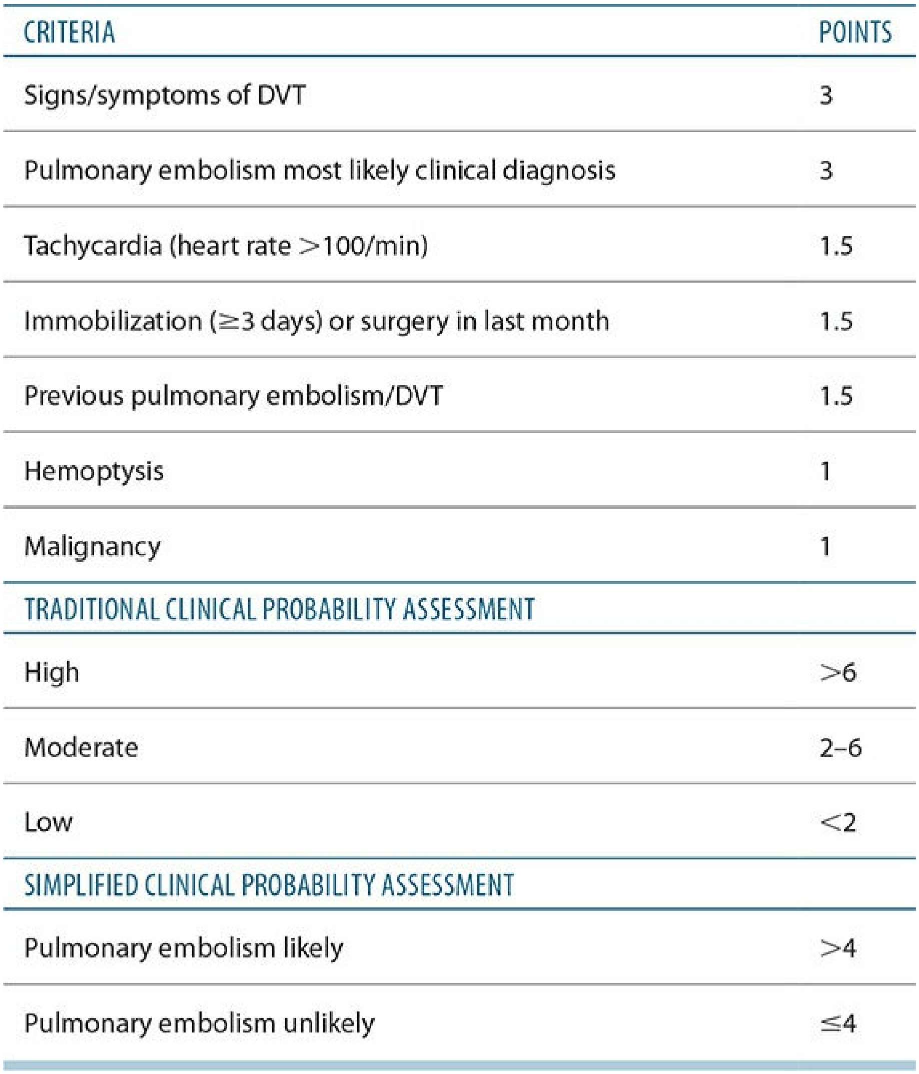
VIRchow triad—risk factors for venous thrombosis:

Vascular trauma
Increased coagulability
Reduced blood flow (stasis)

Diagnosis

- **Best initial step:** Calculation of modified Wells score (Table 2.14-12)

TABLE 2.14-12. **Modified Wells Criteria for Pulmonary Embolism**



CRITERIA	POINTS
Signs/symptoms of DVT	3
Pulmonary embolism most likely clinical diagnosis	3
Tachycardia (heart rate >100/min)	1.5
Immobilization (≥3 days) or surgery in last month	1.5
Previous pulmonary embolism/DVT	1.5
Hemoptysis	1
Malignancy	1
TRADITIONAL CLINICAL PROBABILITY ASSESSMENT	
High	>6
Moderate	2–6
Low	<2
SIMPLIFIED CLINICAL PROBABILITY ASSESSMENT	
Pulmonary embolism likely	>4
Pulmonary embolism unlikely	≤4

- **Pulmonary embolism unlikely (modified Wells score ≤4):**
  - **Best initial test:** D-dimer used to rule out pulmonary embolism; high negative predictive value and sensitivity; not specific. If ↑ D-dimer (≥500 ng/mL) → CT of

chest with contrast (or V/Q scan if unable to obtain CT with contrast). If normal D-dimer → pulmonary embolism excluded.

- **Pulmonary embolism likely (modified Wells score >4):**
  - **Best initial test:** CT of chest with contrast high sensitivity and specificity (see Fig. 2.14-12)

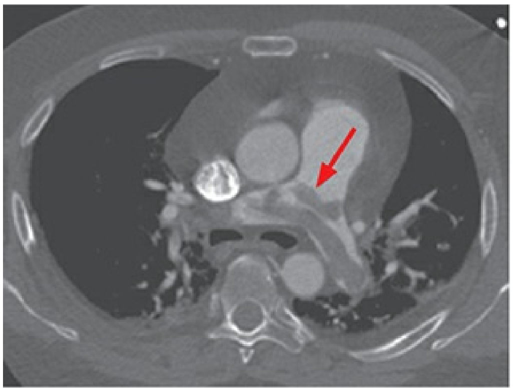


FIGURE 2.14-12. **Pulmonary embolus.** Axial slice from a CT pulmonary angiogram shows a filling defect of the angiogram dye that corresponds to a pulmonary embolus *(red arrow)* extending from the main pulmonary artery into the right and left pulmonary arteries, consistent with a saddle embolus. (Reproduced with permission from Chen MY et al. *Basic Radiology*, 2nd ed. New York, NY: McGraw-Hill; 2011.)

- **Ventilation/perfusion (V/Q) scan:** Used when CT scan is contraindicated (↑ creatinine [(Cr) relative contraindication to contrast], pregnancy [contraindication to radiation]). May reveal areas of V/Q mismatch to predict low, indeterminate, or high probability of pulmonary embolism. A V/Q scan is sensitive for pulmonary embolism but not specific, especially if there is underlying lung disease.
- **ABGs:** Respiratory alkalosis caused by hyperventilation (↓ PaO_2 [<80 mm Hg], ↓ $PaCO_2$).
- **CXR:** May appear normal or show atelectasis, pleural effusion, Hampton hump (a wedge-shaped infarct), or Westermark sign (oligemia/collapse of vessels seen distal to pulmonary embolism).
- **ECG:** Most commonly reveals sinus tachycardia. The classic triad of S1Q3T3 is rare (acute right heart strain with an S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III).
- **Lower extremity venous ultrasound:** Specific and sensitive for DVT, which may be the cause of the pulmonary embolism.

KEY FACT

Dyspnea, tachycardia, and a normal CXR in a hospitalized and/or bedridden patient should raise suspicion of PE.

Treatment

- **Anticoagulation:** See Figure 2.14-13.

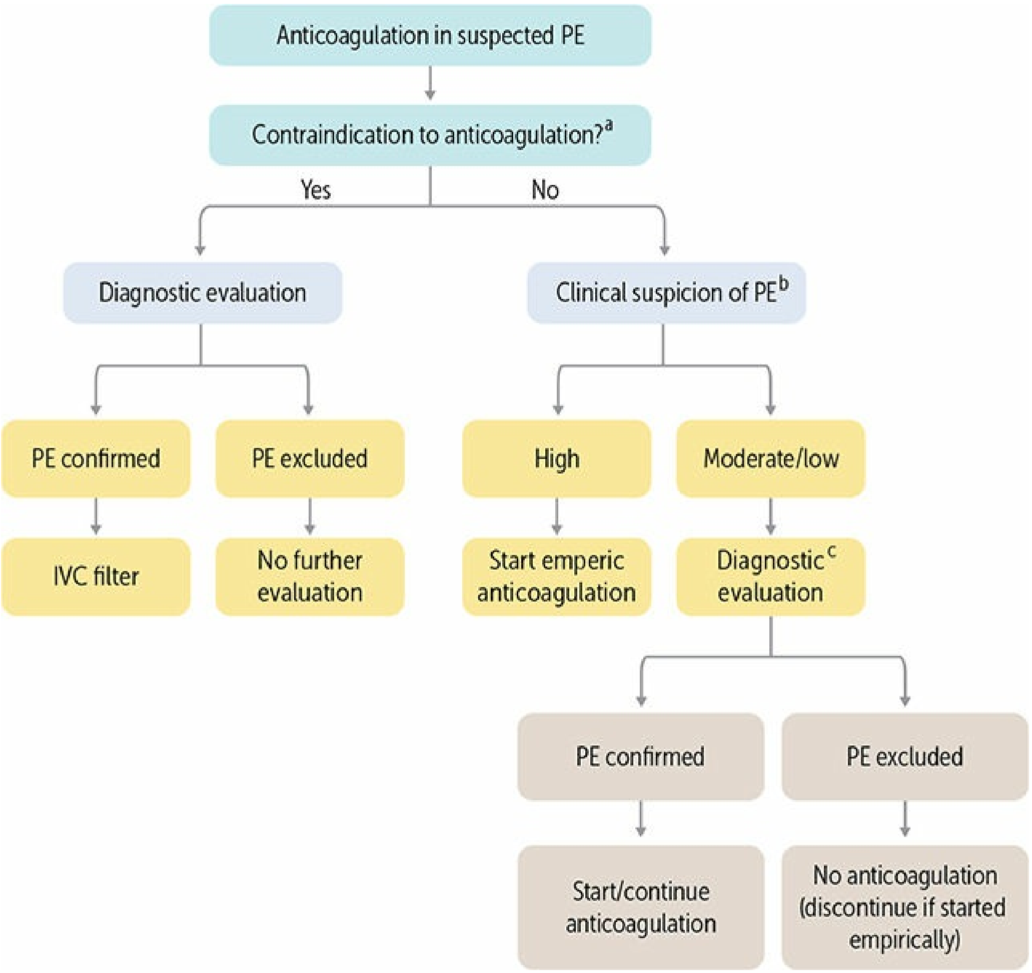

Anticoagulation in suspected PE
Contraindication to anticoagulation?[a]
Yes
No
Diagnostic evaluation
Clinical suspicion of PE[b]
PE confirmed
PE excluded
High
Moderate/low
IVC filter
No further evaluation
Start emperic anticoagulation
Diagnostic[c] evaluation
PE confirmed
PE excluded
Start/continue anticoagulation
No anticoagulation (discontinue if started empirically)

FIGURE 2.14-13. **Guide to anticoagulation in hemodynamically stable patients with a suspected pulmonary embolism (PE).** [a]Contraindications to anticoagulation include recent surgery, hemorrhagic stroke, active bleeding (eg, GI bleed), and aortic dissection. [b]Clinical suspicion of pulmonary embolism is determined using the modified Wells criteria: High >6, moderate 2 to 6, low <2. [c]If diagnostic evaluation cannot be completed within 4 hours, start empiric anticoagulation. (Modified with permission from USMLE-Rx.com.)

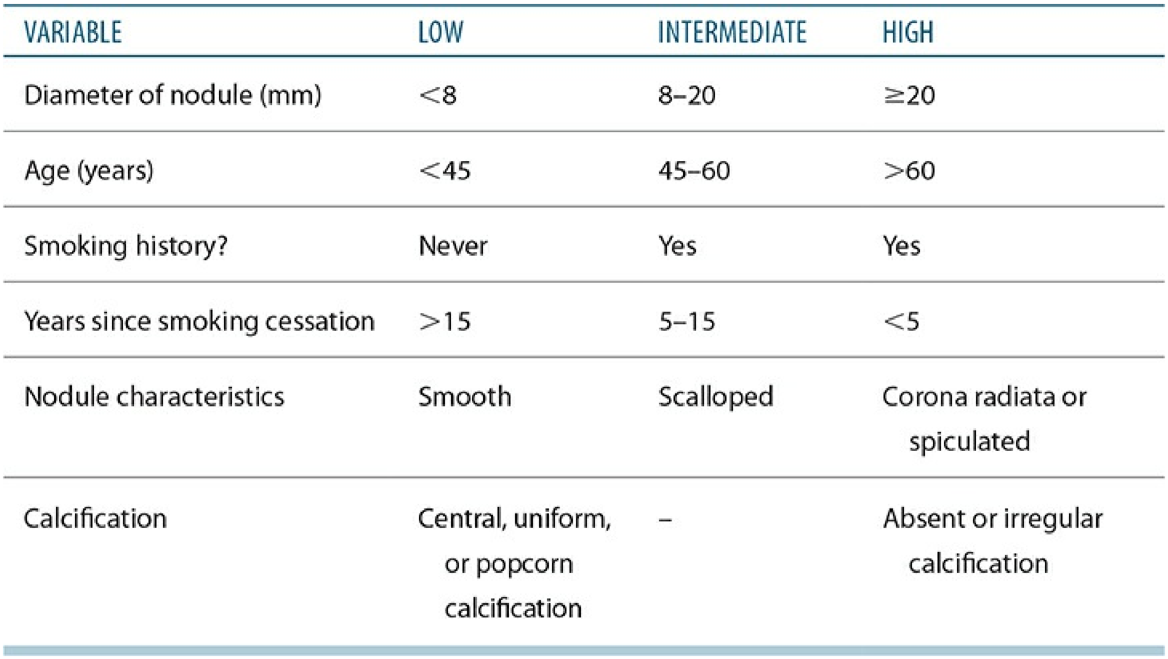
- **Acute:** Unfractionated heparin, subcutaneous low-molecular-weight heparin (LMWH), subcutaneous fondaparinux, or direct oral anticoagulants (rivaroxaban, apixaban). In patients with high probability of pulmonary embolism, anticoagulation should be given before confirmatory testing. Patients with renal failure require unfractionated heparin or apixaban.
- **Chronic:** LMWH, direct oral anticoagulants (preferred), or warfarin (goal for international normalized ratio [INR] = 2–3). Use LMWH in pregnancy (warfarin is contraindicated).
- **Inferior vena cava (IVC) filter:** Indicated in patients with a documented lower extremity DVT/pulmonary embolism if anticoagulation is contraindicated or if patients experience recurrent emboli while on therapeutic doses of anticoagulation.
- **Thrombolysis:** Indicated in cases of massive pulmonary embolism causing right heart failure and hemodynamic instability (saddle pulmonary embolism).
- **DVT prophylaxis:** Treatment for all immobile patients. The physician should prescribe subcutaneous heparin or low-dose LMWH, early ambulation (most effective), and intermittent compression of the lower extremities (less effective).

NEOPLASMS OF THE LUNGS

SOLITARY PULMONARY NODULES

Commonly found on CXR. History, physical exam, and imaging features help guide treatment (see Table 2.14-13).

TABLE 2.14-13. Risk for Malignancy in Patients With Solitary Pulmonary Nodules



VARIABLE	LOW	INTERMEDIATE	HIGH
Diameter of nodule (mm)	<8	8–20	≥20
Age (years)	<45	45–60	>60
Smoking history?	Never	Yes	Yes
Years since smoking cessation	>15	5–15	<5
Nodule characteristics	Smooth	Scalloped	Corona radiata or spiculated
Calcification	Central, uniform, or popcorn calcification	–	Absent or irregular calcification

History/PE

- Often asymptomatic; may present with chronic cough, dyspnea, and shortness of breath.
- Necessary to always inquire about smoking and exposure history, which are associated with ↑ cancer risk.

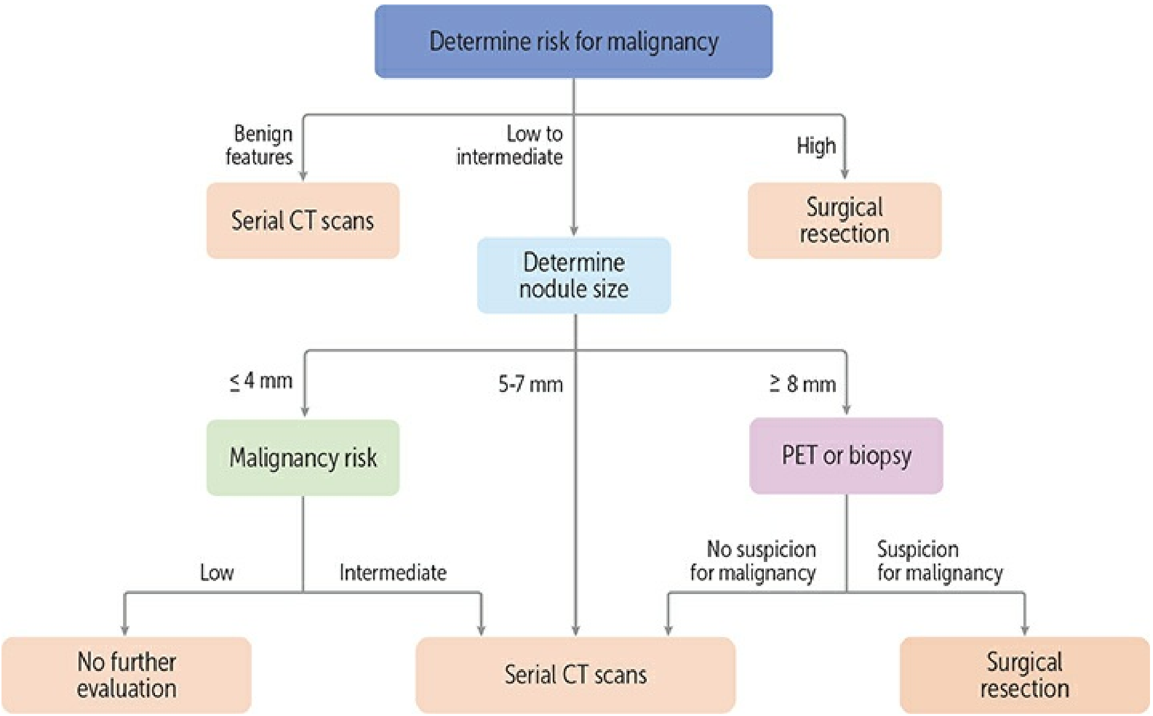
KEY FACT

Lung nodule clues based on history:

- Recent immigrant—think TB
- From the Southwestern United States—think coccidioidomycosis
- From the Ohio River Valley—think histoplasmosis or blastomycosis

Diagnosis and Treatment

Best initial test: CT of the chest. The physician should obtain a noncontrast CT of the chest if a nodule was discovered on another modality (Fig. 2.14-14).



Determine risk for malignancy
Benign features
Low to intermediate
High
Serial CT scans
Surgical resection
Determine nodule size
≤ 4 mm
5-7 mm
≥ 8 mm
Malignancy risk
PET or biopsy
Low
Intermediate
No suspicion for malignancy
Suspicion for malignancy
No further evaluation
Serial CT scans
Surgical resection

FIGURE 2.14-14. **Evaluation of solitary pulmonary nodule detected on CT scan.** (Reproduced with permission from USMLE-Rx.com.)

- If a nodule has fat or calcifications characteristic of a benign lesion (eg, hamartoma, granuloma), no further evaluation is required.
- If a nodule does not have characteristics of a benign lesion, the next step is to review the medical record for a previous CT (if available).
- If the nodule is old and the size is stable (>2 years), no further evaluation is required.
- If the nodule is new, increasing in size, or no prior CT scans are available, then determine risk for malignancy.
- **Low risk:** Serial CT scans.
  - **Intermediate risk:** Further investigation required with biopsy or positron emission tomography (PET).
  - **High risk:** Surgical resection.

LUNG CANCER

The leading cause of cancer death in the United States. Risk factors include tobacco smoke (except for bronchioalveolar carcinoma) and radon or asbestos exposure. Types are as follows (see also Table 2.14-14):

TABLE 2.14-14. **Small Cell and Non–Small Cell Lung Cancers**

TYPE	LOCATION	CHARACTERISTICS	HISTOLOGY
SMALL CELL			
Small cell (oat cell) carcinoma	Central	Central location (Fig. 2.14-15 A and B) Highly correlated with cigarette exposure Undifferentiated and very aggressive; patients have low median survival rate and a poor prognosis Metastases often found on presentation in intrathoracic and extrathoracic sites such as brain, liver, and bone Associated with paraneoplastic syndromes (see Table 2.14-15); may produce **A**CTH (Cushing syndrome), syndrome of inappropriate secretion of ADH (SI**A**DH), or **A**ntibodies against presynaptic Ca^{2+} channels (Lambert-Eaton myasthenic syndrome) or neurons (paraneoplastic myelitis/encephalitis) Rarely operable; treat with radiotherapy (for primary tumour at early stage, and to prevent/palliate brain metastasis), chemotherapy (for metastatic disease)	Neoplasm of neuroendocrine Kulchitsky cells → small, dark blue cells (Fig. 2.14-15 C) Chromogranin A ⊕
NON–SMALL CELL (LESS LIKELY THAN SCLC TO METASTASIZE AT AN EARLY STAGE)			
Adenocarcinoma	Peripheral	Most common lung cancer in female patients, nonsmokers, and overall (except for metastases); activating mutations include *KRAS*, *EGFR*, and *ALK translocation* Associated with hypertrophic osteoarthropathy (clubbing) Bronchioloalveolar subtype (adenocarcinoma in situ): CXR often shows multiple nodules, interstitial infiltration, and prolific sputum production (often confused with pneumonia); good prognosis, ↓ association with smoking; patients have favorable prognosis	Glandular pattern on histology, often stains mucin ⊕ (Fig. 2.14-15 D) Bronchioloalveolar subtype: It grows along alveolar septa, showing apparent "thickening" of alveolar walls
Squamous cell carcinoma	Central	Hilar mass arising from bronchus; cavitation; cigarettes; hypercalcemia (produces PTHrP) strongly associated with smoking	Keratin pearls and intercellular bridges
Large cell carcinoma	Peripheral	High-grade neuroendocrine tumors sharing hallmarks of both small cell and non-small cell lung cancers; poor prognosis; less responsive to chemotherapy; surgical removal	Pleomorphic giant cells
Bronchial carcinoid tumor	—	Favorable prognosis; metastasis rare Symptoms usually caused by mass effect; occasionally carcinoid syndrome (5-hydroxytryptamine [HT] secretion → flushing, diarrhea, wheezing)	Nests of neuroendocrine cells; chromogranin A ⊕

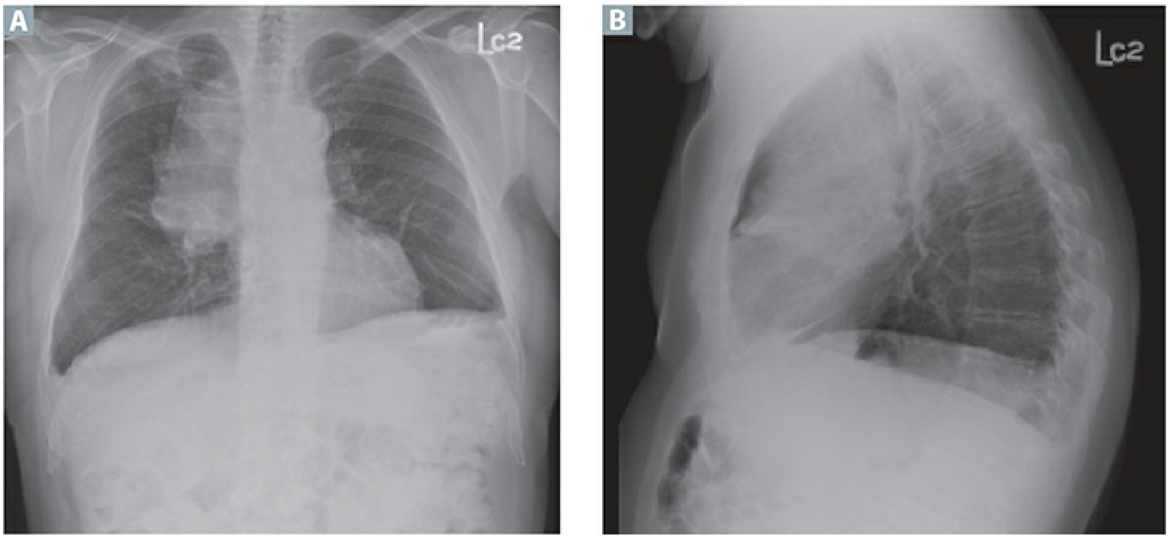


FIGURE 2.14-15. **Histopathology and imaging of lung cancers. A, B, C: Small cell lung cancer.** Note the central location of the tumor in the posteroanterior **(A)** and lateral **(B)** x-rays

of the chest. Histopathology shows clusters of round/oval cells with scant cytoplasm that frequently mold to the neighboring cell **(C)**. Adenocarcinoma of lung: Histopathology **(D)** shows histology of squamous cell carcinoma with prominent nucleoli, mitoses, and necrosis. (Images A and B reproduced with permission from Kantarjian HM et al. MD Anderson Manual of Medical Oncology. New York, NY: McGraw-Hill; 2006. Image C reproduced with permission from Kanchustambham V, Saladi S, Patolia S, Stoeckel D. Spontaneous tumor lysis syndrome in small cell lung cancer. Cureus. 2017;9[2]:e1017. Published 2017 Feb 8. doi:10.7759/cureus.1017. Image D reproduced with permission from Wang JF, Wang B, Jansen JA, et al. Primary squamous cell carcinoma of lung in a 13-year-old boy: a case report. *Cases J.* 2008 Aug 22;1(1):123. doi: 10.1186/1757-1626-1-123.)

MNEMONIC

***S**quamous and **S**mall cell cancers are*
Sentral lesions

MNEMONIC

Lung cancer metastases are often found in LABBs—

Liver
Adrenals
Brain
Bone

Q

A 25-year-old woman presents with dyspnea, chest pain, and leg pain. She takes birth control pills regularly. She returned from Asia 3 days ago. What is the next step?

History/PE

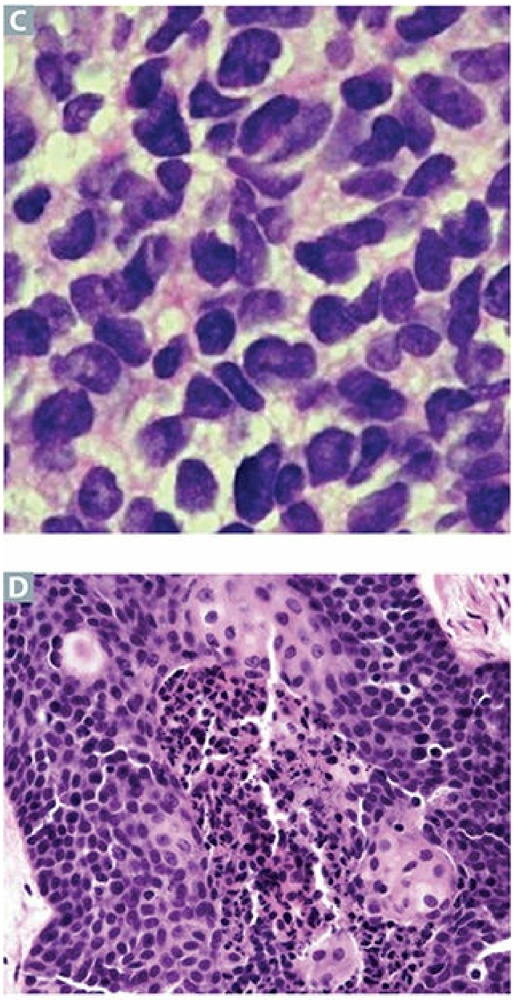
- **Presentation:** Cough, hemoptysis, dyspnea, wheezing, pneumonia, chest pain, weight loss, and possible abnormalities on respiratory exam (crackles, atelectasis)

A

The next step is to treat with a heparin bolus or low-molecular-weight heparin (LMWH). When there is high clinical suspicion (birth control, history of long flight, multiple symptoms) for a DVT/PE, one should treat first and follow with imaging (CT angiogram). With patients who have lower clinical suspicion, imaging is warranted first before treatment.

- **Superior sulcus tumors** (**Pancoast tumors**)**:** Tumor at the apex of the lung, adjacent to the subclavian vessels; presentation is dependent on which of the following structures are compressed:
    - **Brachial plexus:** Shoulder pain (most common initial symptom) and arm pain (C8–T2 radicular pain)
    - **Paravertebral sympathetic chain and inferior cervical (stellate) ganglion:** Horner syndrome (miosis, ptosis, anhidrosis)

- **Superior vena cava (SVC) syndrome:** Obstruction of the SVC with supraclavicular venous engorgement and facial swelling (see Fig. 2.14-16)



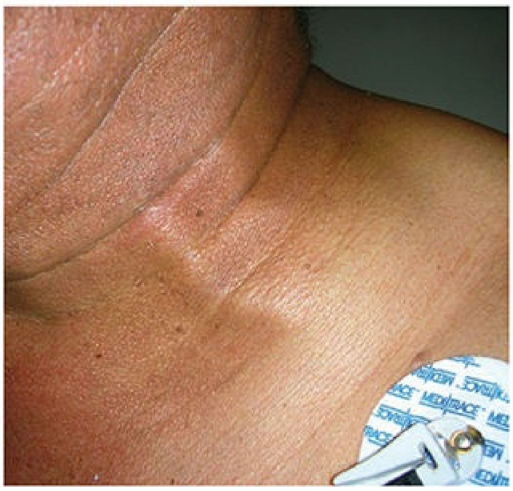
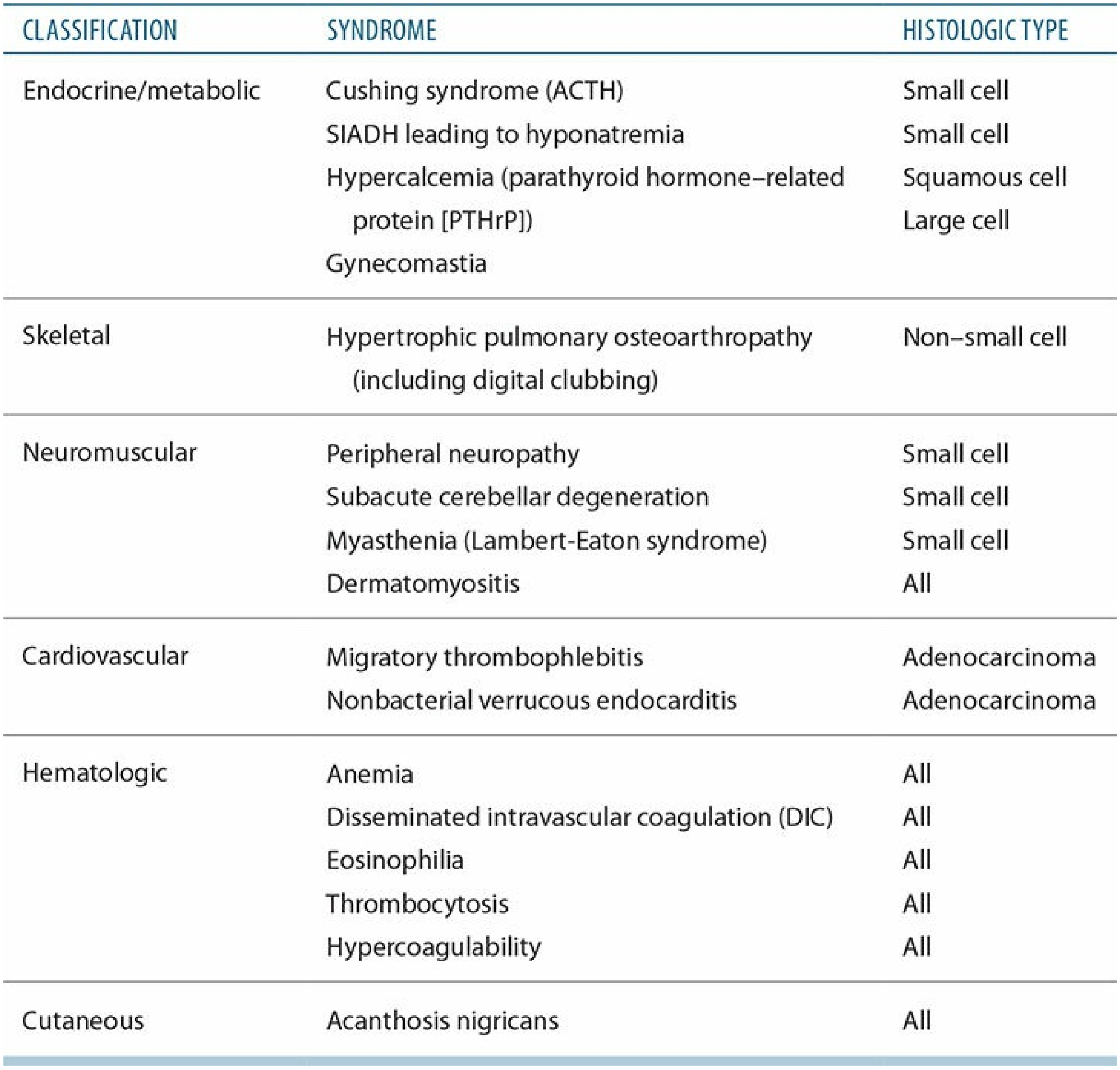


FIGURE 2.14-16. SVC syndrome. Prominent JVD is seen in SVC syndrome secondary to obstruction of the SVC by a central malignant lesion. (Reproduced with permission from Tintinalli JE et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 7th ed. New York, NY: McGraw-Hill; 2011.)

- **Hoarseness:** Secondary to recurrent laryngeal nerve involvement

- Many paraneoplastic syndromes (see Table 2.14-15)

TABLE 2.14-15. **Paraneoplastic Syndromes of Lung Cancer**



CLASSIFICATION	SYNDROME	HISTOLOGIC TYPE
Endocrine/metabolic	Cushing syndrome (ACTH)	Small cell
	SIADH leading to hyponatremia	Small cell
	Hypercalcemia (parathyroid hormone–related protein [PTHrP])	Squamous cell Large cell
	Gynecomastia	
Skeletal	Hypertrophic pulmonary osteoarthropathy (including digital clubbing)	Non–small cell
Neuromuscular	Peripheral neuropathy	Small cell
	Subacute cerebellar degeneration	Small cell
	Myasthenia (Lambert-Eaton syndrome)	Small cell
	Dermatomyositis	All
Cardiovascular	Migratory thrombophlebitis	Adenocarcinoma
	Nonbacterial verrucous endocarditis	Adenocarcinoma
Hematologic	Anemia	All
	Disseminated intravascular coagulation (DIC)	All
	Eosinophilia	All
	Thrombocytosis	All
	Hypercoagulability	All
Cutaneous	Acanthosis nigricans	All

Diagnosis

- **Best initial test:** CXR or CT of the chest
- If initial test raises suspicion for malignancy, the physician should obtain a tissue sample next
- **Most accurate tests:** Fine-needle aspiration (CT guided) for peripheral lesions and bronchoscopy (biopsy or brushing) for central lesions
- Once diagnosis established, PET/CT is done for staging.

Treatment

Treatment of small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC) varies according to the stage. Early-stage diseases require surgery with or without neoadjuvant/adjuvant therapy (chemotherapy, immunotherapy, radiotherapy).

Given prior to surgery, neoadjuvant therapy aims to decrease the size of a tumor. Adjuvant therapy is given right after surgery to decrease chances for residual disease.

For advanced-stage disease, systemic therapy is the best recommended approach. For some inoperable tumours (Stage III) or in patients unfit for surgery, chemotherapy and radiation alone may sometimes be curative. The regimens of systemic therapies differ according to the histology, but the principles remain the same.

Q

A 65-year-old patient with a 30-pack-year history presents with a 2-week history of facial swelling. CT imaging reveals a hilar mass and biopsy reveals SCLC. What is the next step in treatment?

Types of systemic therapies include:

- **Chemotherapy:** Aims to kill rapidly dividing cells. It is an imprecise way of preventing cancer growth. However, chemotherapy prevents growth of not only cancer cells but also normal cells of the GI tract and others. It can therefore cause adverse events such as diarrhea, nausea, and hair loss.
- **Targeted therapy:** Aims to block cancer cells harboring a driver mutation (eg, *EGFR* mutation or *ALK* translocation).
- **Immunotherapy:** Aims to activate the immune system to fight cancer cells. Examples are immune checkpoint inhibitors (eg, anti-programmed death [PD]-1 inhibitors, anti–programmed death-ligand 1 [PD-L1] inhibitors, and anti-cytotoxic T-lymphocyte–associated antigen 4 [anti-CTLA-4]). PD-1 and CTLA4 are checkpoint regulators present on immune cells. When PD-1 is bound to its ligands (present on the cancer cells), it prevents activation of the immune system.

RESPIRATORY TRACT INFECTIONS

Note: Epiglottitis, laryngotracheobronchitis, and bronchiolitis are mostly seen in infants—please refer to the Pediatrics chapter for a discussion of these entities.

PNEUMONIA

Bacterial, fungal, or viral infection of the parenchyma of the lung.

A

The mainstay of therapy for SCLC is chemotherapy, which yields high rates of response. It is the next step in treatment.

History/PE

Living conditions and social history in the weeks preceding presentation, comorbidities, and history of hospitalizations can all give important clues to determine the most likely pathogens.

- **Classic presentation:** Acute onset of fever, productive cough (purulent yellow-green sputum or hemoptysis), dyspnea, night sweats, and pleuritic chest pain. Symptoms may be subtle in immunocompromised/older adult patients.
- Atypical presentations (gradual onset, dry cough, headaches, myalgias, sore throat, GI symptoms) can be seen with viral pneumonias and infections with fastidious organisms

(*Legionella pneumophila*, *Mycoplasma pneumoniae*, *C pneumoniae*).

- Lung examination may show ↓ or bronchial breath sounds, rales, wheezing, dullness to percussion, egophony, and/or tactile fremitus.

Diagnosis

The diagnosis of pneumonia is made in the setting of a suspicious clinical context and compatible chest imaging findings.

- CXR is the best initial diagnostic test (see figure 2.14-17). If CXR does not reveal clear infiltrate but suspicion for pneumonia is high, a noncontrast CT of the chest can be obtained for more detailed visualization of the lung parenchyma.

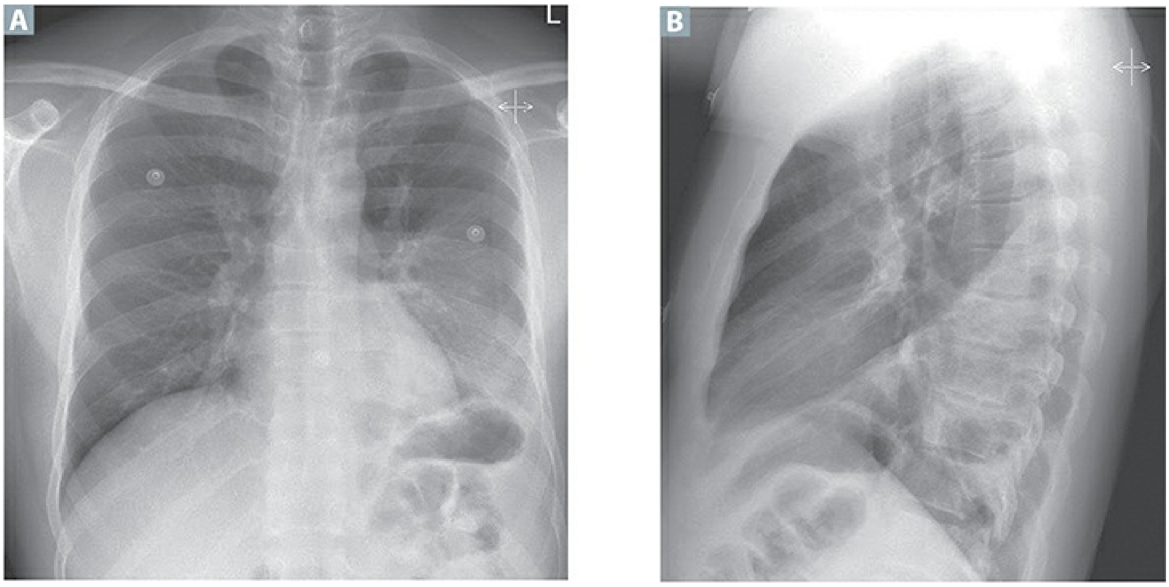


FIGURE 2.14-17. **Lobar pneumonia.** Posteroanterior **(A)** and lateral **(B)** CXRs of a 41-year-old man with cough and shortness of breath show a left lower lobe opacity consistent with lobar pneumonia. *Streptococcus pneumoniae* was confirmed by sputum Gram stain and culture. (Reproduced with permission from USMLE-Rx.com.)

- Severity of illness determines best management setting (inpatient vs outpatient) and recommended diagnostic workup. Routine bloodwork (CBC, metabolic panel) should be obtained for all patients.
- For patients treated in the outpatient setting, influenza testing can be considered if they are candidates for antiviral treatment with oseltamivir. Otherwise, no additional workup is needed unless there is failure to respond to initial treatment or if there are risk factors for resistant organisms (recent hospitalization, structural lung disease).
- For patients treated in the hospital, blood cultures and sputum Gram stain (see Fig. 2.14-18) and culture are indicated, as well as respiratory viral testing, *Legionella* testing, and urine streptococcal antigen testing.

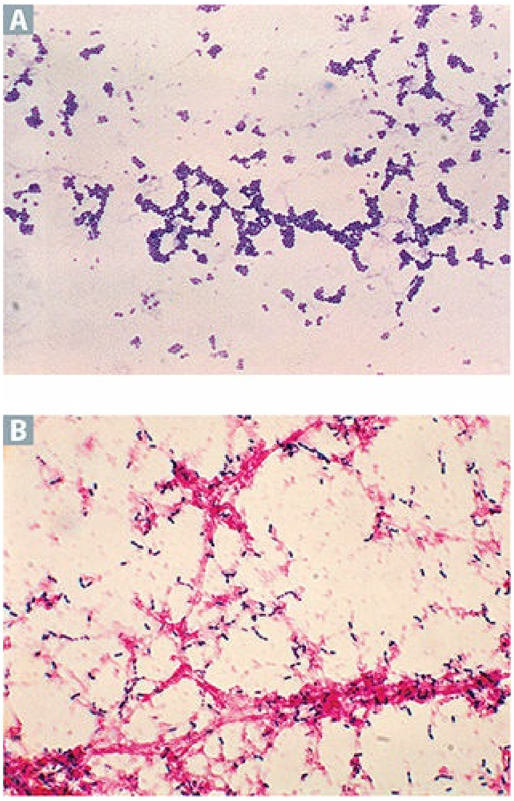


FIGURE 2.14-18. **Common pathogens causing pneumonia**. **(A)** *Staphylococcus aureus.* These clusters of gram ⊕ cocci were isolated from the sputum of a patient who developed pneumonia while hospitalized. **(B)** *Streptococcus pneumoniae.* Sputum sample from a patient with pneumonia. Note the characteristic lancet-shaped gram ⊕ diplococci. Image A reproduced with permission from Dr. Richard Facklam, Centers for Disease Control and Prevention, Atlanta, GA. Image B reproduced with permission from Dr. Mike Miller, Centers for Disease Control and Prevention, Atlanta, GA.

- Testing for “atypical” organisms—those that are difficult to culture on standard culture media—can be considered if clinical suspicion is high.

Q

A 70-year-old man presents to the emergency department with 5 days of fever, productive cough, and altered mental status. He is also found to be hypotensive and tachypneic. Broad-spectrum antibiotics and fluid resuscitation are promptly administered, but the patient continues to be hypotensive. What is the next best step in treatment?

Clinical and social context is important when trying to determine the most likely pathogen in a patient with pneumonia. Common causes of pneumonia are outlined in Tables 2.14-16 and 2.14-17 and illustrated in Figure 2.14-18.

TABLE 2.14-16. **Causes of Pneumonia by Category**

CATEGORY	ETIOLOGY
Typical bacteria	*Streptococcus pneumoniae, H influenzae, Moraxella catarrhalis, Staphylococcus aureus, group A Streptococcus*
Atypical bacteria	*Legionella, M pneumoniae, C pneumoniae, Chlamydia psittaci*
Respiratory viruses	Influenza A and B, SARS-CoV-2 and other coronaviruses, rhinoviruses, parainfluenza viruses, adenoviruses

TABLE 2.14-17. **Causes of Pneumonia by Risk Factors and Associated Conditions**

CONDITIONS	ETIOLOGY
Alcohol use disorder	*S pneumoniae, Klebsiella, Acinetobacter,* oral anaerobes
Aspiration	Enteric gram negatives and oral anaerobes
COPD	*H influenzae, Moraxella catarrhalis, S pneumoniae, Pseudomonas, Legionella*
Exposure to animals	Birds: Avian influenza, *C psittaci*. Birds or bats: *Histoplasma capsulatum*. Rabbits: *Francisella tularensis*. Farm animals: *Coxiella burnetiid*
HIV	*S pneumoniae, H influenzae, Mycobacterium tuberculosis* (particularly in early infection), *Pneumocystis jirovecii, Cryptococcus, Histoplasma, Aspergillus,* atypical mycobacteria, *Pseudomonas*
Recent travel	Hotel or cruise: *Legionella*. Southwest United States: *Hantavirus, Coccidioides*. Southeast/East Asia: *Burkholderia pseudomallei*. Middle East: MERS coronavirus
Structural lung disease	*Pseudomonas, Burkholderia cepacia, S aureus*
Postviral	*Staphylococcus, S pneumoniae, H influenzae*
Injection drug use	*S aureus*, anaerobes, *Mycoplasma tuberculosis, S pneumoniae*
Endobronchial obstruction	*S pneumoniae, H influenzae, S aureus,* anaerobes

Treatment

Empiric antibiotic choice is also determined by illness severity and local antibiotic sensitivity. If a specific pathogen is identified in diagnostic testing, antibiotic therapy should then be tailored to target it.

Immunocompromised patients and those with structural lung disease (bronchiectasis, CF) have a higher risk of developing *Pseudomonas* pneumonia—consider activity against this pathogen by using an antipseudomonal β-lactam (eg, piperacillin-tazobactam) plus either a respiratory fluoroquinolone or a macrolide.

A summary of the recommended **best initial treatment** for pneumonia is given in Table 2.14-18.

TABLE 2.14-18. Treatment of Pneumonia

PATIENT TYPE	SUSPECTED PATHOGENS	EMPIRIC COVERAGE
Those with outpatient community-acquired pneumonia, ≤65 years of age, otherwise healthy, no antimicrobials within 3 months	*S pneumoniae, M pneumoniae, C pneumoniae, H influenzae,* viral	Amoxicillin, doxycycline, or macrolide (if local pneumococcal resistance is <25%)
>65 years of age or comorbidity (COPD, heart failure, renal failure, diabetes, liver disease, ethanol [EtOH] abuse) or antimicrobial use within 3 months	*S pneumoniae, H influenzae,* aerobic gram-negative rods ([GNRs], eg, *E coli, Enterobacter, Klebsiella), S aureus, Legionella,* viruses	Combination of amoxicillin/clavulanate or cephalosporin + macrolide or doxycycline OR respiratory fluoroquinolone monotherapy
Patients with community-acquired pneumonia requiring hospitalization	*S pneumoniae, H influenzae,* anaerobes, aerobic GNRs, *Legionella, Chlamydia*	Respiratory fluoroquinolone OR β-lactam + macrolide
Community-acquired pneumonia requiring ICU care	*S pneumoniae, Legionella, H influenzae,* anaerobes, aerobic GNRs, *Mycoplasma, Pseudomonas*	β-Lactam + macrolide OR β-lactam + fluoroquinolone
Patients with hospital-acquired pneumonia	GNRs (including *Pseudomonas* and *Acinetobacter*), *S aureus, Legionella,* mixed flora	Antipseudomonal agent to start If structural lung disease is present, addition of second antipseudomonal agent If patient is critically ill (in shock or requiring ventilatory support due to pneumonia), the physician should use two antipseudomonal agents plus an anti-MRSA agent

KEY FACT

The pneumococcal vaccine should be given to all children and to patients >65 years of age. Other indications for pneumococcal vaccine include chronic heart/lung/liver disease, chronic renal failure, diabetes, cigarette smoking, asplenia, immunocompromise (congenital immunodeficiency, malignancy), asplenia, cerebrospinal fluid (CSF) leaks, and cochlear implants.

A

The next best step in treatment entails administration of vasopressors and ICU admission. This patient is in septic shock, probably secondary to pneumonia. Patients with pneumonia who require vasopressors or mechanical ventilation warrant admission to an ICU.

INFLUENZA

A highly contagious orthomyxovirus transmitted by droplet nuclei. There are three types of influenza: A, B, and C. Subtypes of influenza A (eg, H5N1, H1N1) are classified based on glycoproteins (hemagglutinin [H] and neuraminidase [N]). Relevant terms are as follows:

- **Antigenic drift:** Refers to small, gradual changes in surface proteins through point mutations. These small changes are sufficient to allow the virus to escape immune recognition, accounting for why individuals can be infected with influenza multiple times.
- **Antigenic shift:** Describes an acute, major change in the influenza A subtype (significant genetic reassortment) circulating among humans. Leads to pandemics.

In the United States, the typical influenza season begins in November and lasts until April. Yearly vaccination with inactivated influenza virus is currently recommended for all patients ≥6 months of age. Children 6 months to 8 years of age require two doses of the seasonal vaccine if they are receiving the vaccine for the first time. A high-dose flu vaccine is available for people ≥65 years of age or those who are immunocompromised.

History/PE

Patients typically present with abrupt onset of fever, myalgia, chills, cough, coryza, and weakness. Older adult patients may have atypical presentations characterized only by confusion.

Diagnosis

- **Best initial test:** Rapid influenza test of viral antigens from nasopharyngeal swab.
- **Most accurate test:** Diagnosis can be made with direct fluorescent antibody (DFA) tests, viral culture, or PCR assays. Rapid influenza tests have low sensitivity, and influenza is usually a clinical diagnosis. Leukopenia is a common finding.

Treatment

- Analgesics and hydration provide symptomatic care.
- Antivirals such as oseltamivir or zanamivir are most effective when used within 2 days of onset and may shorten the duration of infection by 1 to 3 days.

Complications

Severe primary viral pneumonia with ARDS, secondary bacterial pneumonia (see “Postviral” in Table 2.14-20), sinusitis, bronchitis, and exacerbation of COPD and asthma can occur.

ASPERGILLOSIS

A group of diseases caused by *Aspergillus*, typically *Aspergillus fumigatus*, through infection by spores. *Aspergillus* can be seen on silver stain as acutely (<45 degrees) branched septate hyphae.

Allergic Bronchopulmonary Aspergillosis

Hypersensitivity reaction seen in people with asthma or CF. Refer to the Restrictive Lung Disease section of this chapter.

Aspergilloma

Typically discovered as an incidental radiographic finding in patients with preexisting lung disease (eg, TB, COPD).

- ***Hx/PE:*** May be asymptomatic or present with hemoptysis. Fever and cough are less common.
- ***Dx:*** CXR or CT reveals a solid mass within a preexisting lung cavity (Fig. 2.14-19).

Laboratory tests are typically normal.

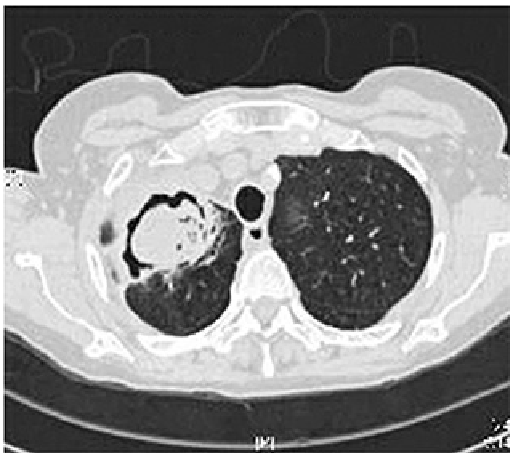


FIGURE 2.14-19. **Chronic aspergilloma.** Intracavitary mass with surrounding "air crescent". The mass may move with change in posture. (Reproduced with permission from Farid S, Mohamed S, Devbhandari M, et al. Results of surgery for chronic pulmonary aspergillosis, optimal antifungal therapy and proposed high risk factors for recurrence: a national centre's experience. *J Cardiothorac Surg*. 2013;8[180]. https://doi.org/10.1186/1749-8090-8-180.)

- ***Tx:*** Antifungals are not very effective. If symptomatic, curative surgical resection or embolization for hemoptysis can be pursued.

Chronic Necrotizing Pulmonary Aspergillosis

Rare, antibiotic-resistant pneumonia that occurs in patients with immunosuppression (eg, alcohol use disorder, steroid-dependent COPD).

- ***Hx/PE:*** Fever, cough, hemoptysis, night sweats, fatigue.
- ***Tx:*** Voriconazole (or other triazole); rarely surgical resection can be performed if localized and severe disease.

Invasive Pulmonary Aspergillosis

Severe, rapidly progressive infection that occurs in profoundly immunosuppressed patients (eg, chemotherapy, transplant). Infection begins in the respiratory tract and then disseminates hematogenously (angioinvasion leading to septic emboli).

- ***Hx/PE:*** Fever, cough, pleuritic chest pain, tachypnea/hypoxemia.
- ***Dx:*** Serum galactomannan assay. If negative but degree of suspicion is high, bronchoscopy with bronchoalveolar lavage sent for galactomannan and *Aspergillus* PCR or lung biopsy can be considered.
- ***Tx:*** Voriconazole (or other triazole) in addition to decreasing immunosuppression.

HISTOPLASMOSIS

Risk factors include HIV/AIDS, spelunking (exploring caves), and exposure to bird or bat excrement, especially in the Ohio and Mississippi river valleys (see Fig. 2.14-20).

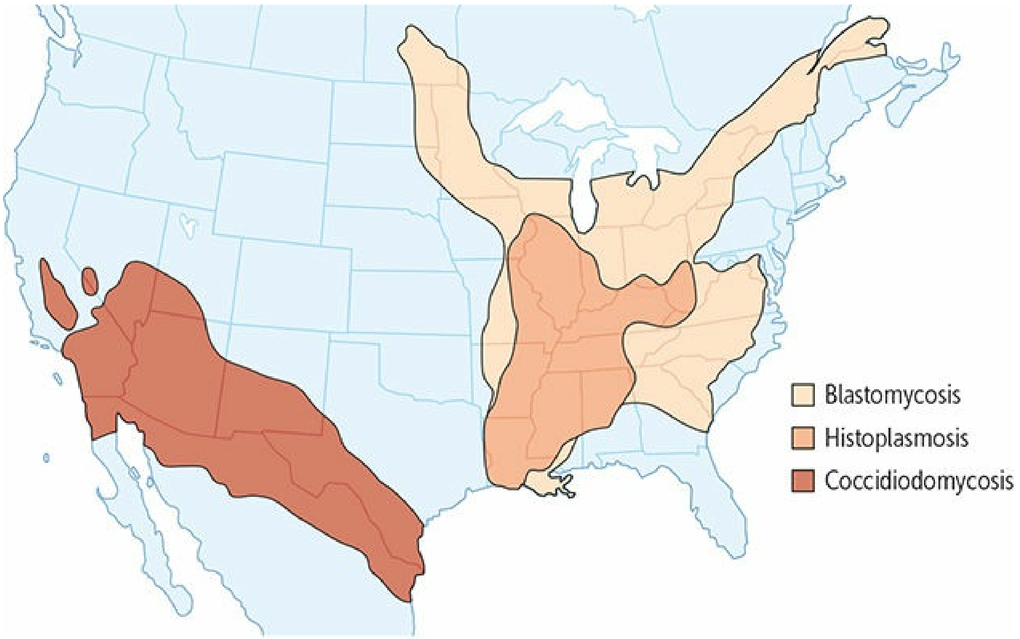


FIGURE 2.14-20. **Geographic distribution of systemic fungal infection in the United States.** (Reproduced with permission from Ryan KJ, Ray CG. *Sherris Medical Microbiology*, 5th ed. New York, NY: McGraw-Hill; 2010.)

History/PE

- Primary exposure is often asymptomatic or causes a flulike illness.
- Presentation may range from no symptoms to fulminant disease with pulmonary and/or extrapulmonary manifestations.
- Fever, weight loss, hepatosplenomegaly, lymphadenopathy, nonproductive cough, palatal or tongue ulcers, and pancytopenia indicate disseminated infection (most often within 14 days).
- The differential diagnosis includes atypical bacterial pneumonia, blastomycosis, coccidioidomycosis, tuberculosis (TB), sarcoidosis, pneumoconiosis, and lymphoma (see Table 2.14-18).

TABLE 2.14-18. **Differential Diagnosis of Opportunistic Pulmonary Fungal Infections**

	HISTOPLASMOSIS	COCCIDIOIDOMYCOSIS	BLASTOMYCOSIS
Disseminated disease	Hepatosplenomegaly, lymphadenopathy, nonproductive cough	Meningitis, bone lesions, abscesses, erythema nodosum	Meningitis; bone, prostate, and skin lesions; ARDS
Diagnosis	Urine and serum polysaccharide antigens	PCR assay of bronchoalveolar lavage and tissue samples	Culture showing broad-based budding yeast

Diagnosis

- CXR shows diffuse nodular densities, focal infiltrate, cavity, and/or hilar lymphadenopathy (chronic infection is usually cavitary).
- Urine and serum polysaccharide antigen tests are the most sensitive for making the **initial diagnosis** of disseminated disease, monitoring response to therapy, and diagnosing

relapse. Culture is also diagnostic (blood, sputum, bone marrow, cerebrospinal fluid [CSF]).

- The yeast form is seen with special stains on biopsy (bone marrow, lymph node, liver) or bronchoalveolar lavage (see Fig. 2.14-21).

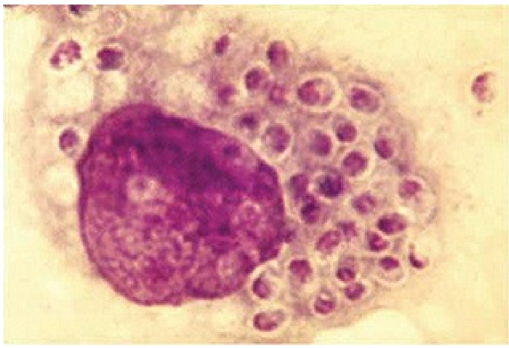


FIGURE 2.14-21. **Histiocyte macrophage containing numerous yeast cells of *Histoplasma capsulatum* (Giemsa stain).** (Adapted with permission from Dr. J.T. McClellan and the Centers for Disease Control and Prevention, Lexington, KY.)

Treatment

- **Mild pulmonary disease or stable nodules:** Treat supportively in the immunocompetent host. Consider itraconazole.
- **Chronic cavitary lesions:** Give itraconazole for >1 year.
- **Severe acute pulmonary disease or disseminated disease:** Liposomal amphotericin B **or** amphotericin B for 14 days, followed by itraconazole for 1 year or longer. Lifelong maintenance therapy with daily itraconazole may be necessary.

KEY FACT

Nocardia is a partially acid-fast, gram ⊕, branching rod found in soil that is a common cause of lung and CNS infection in immunocompromised hosts. Trimethoprim-sulfamethoxazole (TMP-SMX) is the treatment of choice (see Fig. 2.14-22).

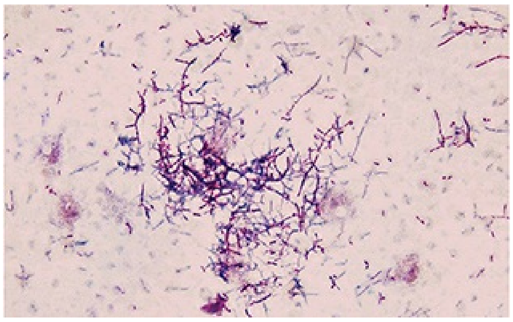


FIGURE 2.14-22. **Nocardia.** Branching filaments on acid-fast stain. (Modified with permission from Leli C et al. Fatal Nocardia farcinica bacteremia is diagnosed by matrix-assisted laser desorption-ionization time of flight mass spectrometry in a patient with myelodysplastic syndrome treated with corticosteroids. *Case Rep Med.* 2013;2013:368637.)

COCCIDIOIDOMYCOSIS

A pulmonary fungal infection endemic to the Southwestern United States (Fig. 2.14-20). Can present as an acute or subacute pneumonia or as a flulike illness and may involve extrapulmonary sites, including bone, CNS, and skin (manifestations include erythema multiforme or erythema nodosum). The incubation period is 1 to 4 weeks after exposure. Pregnant, HIV ⊕ patients, and those of Filipino or African descent are at ↑ risk for disseminated disease.

History/PE

Patients present with fever, anorexia, headache, chest pain, cough, dyspnea, arthralgias, and night sweats. Disseminated infection can present with meningitis, bone lesions, and soft tissue abscesses.

Diagnosis

- Serology is specific but not sensitive during the first 1 to 2 weeks after infection. Repeat testing can increase sensitivity, and the disease can be confirmed with immunodiffusion testing.
- PCR assays of respiratory specimens have been developed that are highly sensitive and specific.
- The physician should obtain bronchoalveolar lavage and fungal cultures of sputum, wound exudate, or other affected tissue. Cultures are usually only obtained in hospitalized patients or patients with severe disease, and growth can take days to weeks.
- Identification of *Coccidioides immitis* spherules can occur with hematoxylin and eosin (H&E) stain or other special sputum or tissue stains.
- CXR findings may be normal or show infiltrates, nodules, cavities, mediastinal or hilar adenopathy, or pleural effusion.

KEY FACT

Consider coccidioidomycosis in a patient from the Southwestern United States who presents with respiratory infection. Pregnant and HIV ⊕ patients and those of Filipino and African descent are at ↑ risk for disseminated disease.

Treatment

- **Acute:** PO fluconazole or itraconazole for mild infection. IV amphotericin B is only for severe or protracted primary pulmonary infection and disseminated disease, followed by PO azole therapy once stable.
- **Chronic:** No treatment needed for asymptomatic chronic pulmonary nodules or cavities. Progressive cavitary or symptomatic disease usually requires surgery plus long-term azole therapy for 8 to12 months.

BLASTOMYCOSIS

A fungal infection endemic to the central and southeastern United States, particularly the Mississippi and Ohio river valleys.

- ***Hx/PE:*** Presents similarly to coccidioidomycosis and typically has extrapulmonary involvement in the bone, prostate, and skin.
- ***Dx:*** Serologic tests not sensitive enough. Culture is the only way to definitively diagnose, and a sputum smear will show broad-based budding yeast.
- ***Tx:*** Treat symptomatic patients with itraconazole and consider inpatient treatment with amphotericin B and intensive care unit (ICU) admission if the condition is complicated by

ARDS, meningitis, or other systemic involvement.

MYCOBACTERIAL INFECTIONS

TUBERCULOSIS

Infection caused by *Mycobacterium tuberculosis*. Roughly 2 billion people are infected with TB (global prevalence). In the United States, close to 10,000 new TB disease cases are identified per year.

History/PE

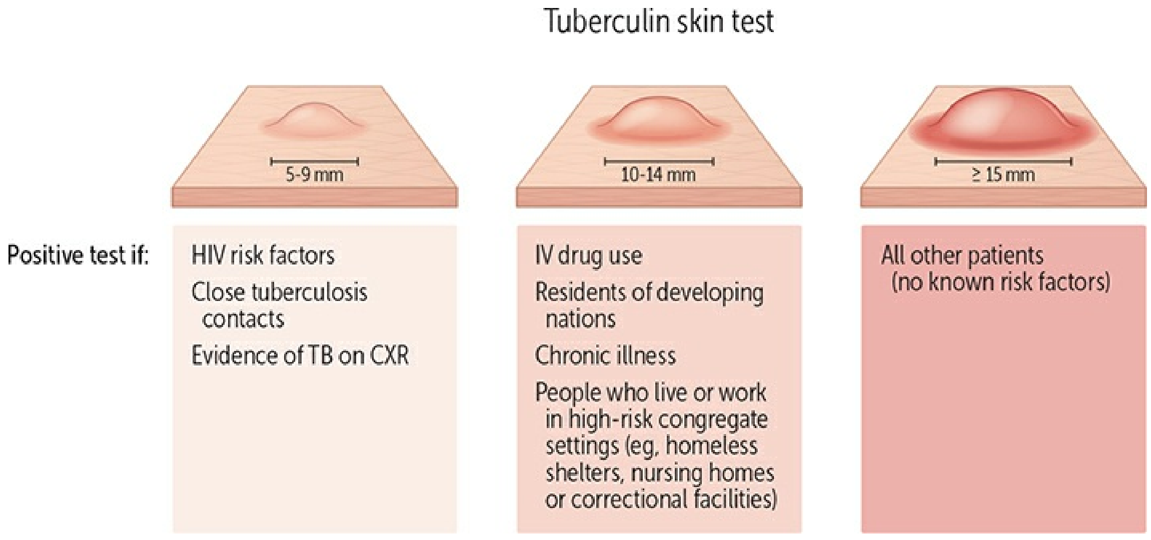
- The physician should identify risk factors for TB in a patient’s history, including history of travel to and from high-risk nations (particularly prevalent in Southeast Asia and sub-Saharan Africa), homelessness, incarceration, alcohol use disorder, IV drug use, HIV positivity, and employment in healthcare. Pre-existing lung disease, immunosuppression, and advancing age are also risk factors.
- Most people who become infected with TB are asymptomatic (latent TB). Symptomatic patients can present as primary or secondary (ie, reactivation of latent) TB.
- Most cases of TB are confined to the lungs—presenting signs include cough, hemoptysis, dyspnea, pleuritic chest pain, fever, weight loss, night sweats, and fatigue. Extrapulmonary TB (more common in patients with HIV) spreads hematogenously and can affect any organ system.

KEY FACT

Management of the Mantoux tuberculin skin test is the same for patients regardless of Bacillus Calmette–Guérin (BGC) vaccination status, but testing with interferon-gamma release assays is preferred for those who have received the BCG vaccine.

Diagnosis

- **Latent disease (asymptomatic and previous exposure):** Diagnose with a ⊕ tuberculin skin test ([TST], see Fig. 2.14-23) or interferon-gamma release assay (IGRA).



Positive test if:	HIV risk factors Close tuberculosis contacts Evidence of TB on CXR	IV drug use Residents of developing nations Chronic illness People who live or work in high-risk congregate settings (eg, homeless shelters, nursing homes or correctional facilities)	All other patients (no known risk factors)

FIGURE 2.14-23. Purified protein derivative (PPD) interpretation. (Reproduced with permission from USMLE-Rx.com.)

- Immunocompromised individuals with latent TB infection may have a ⊖ TST (anergy).
- All patients with a ⊕ purified protein derivative (PPD) require evaluation with a CXR to rule out active disease.
- **Active disease:** Mycobacterial culture of sputum (or blood/tissue for extrapulmonary disease) is the most accurate test but can take weeks to obtain. A sputum acid-fast stain (see Fig. 2.14-24) can yield rapid preliminary results. It is the best initial test, but it lacks sensitivity. Testing of three specimens, obtained 8 hours apart, is recommended. If stains are positive, NAAT and culture are recommended. If extrapulmonary TB is suspected, samples should be sent from affected sites.

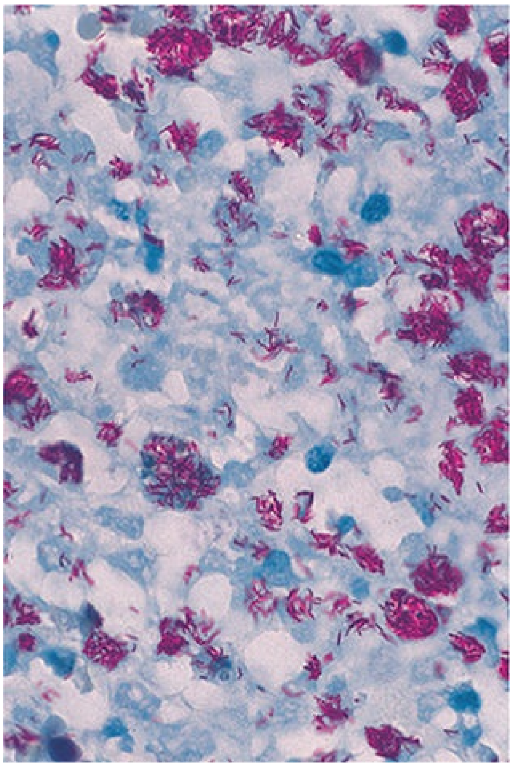


FIGURE 2.14-24. Tuberculosis. Note the red color (“red snappers”) of tubercle bacilli on acid-fast staining. (Reproduced with permission from Milikowski C. *Color Atlas of Basic Histopathology*. Stamford, CT: Appleton & Lange; 1997.)

- The most common finding among typical hosts is a cavitary infiltrate in the upper lobe on CXR (see Fig. 2.14-25), which may be accompanied by calcification of one or more nearby lymph nodes (Ghon complex).

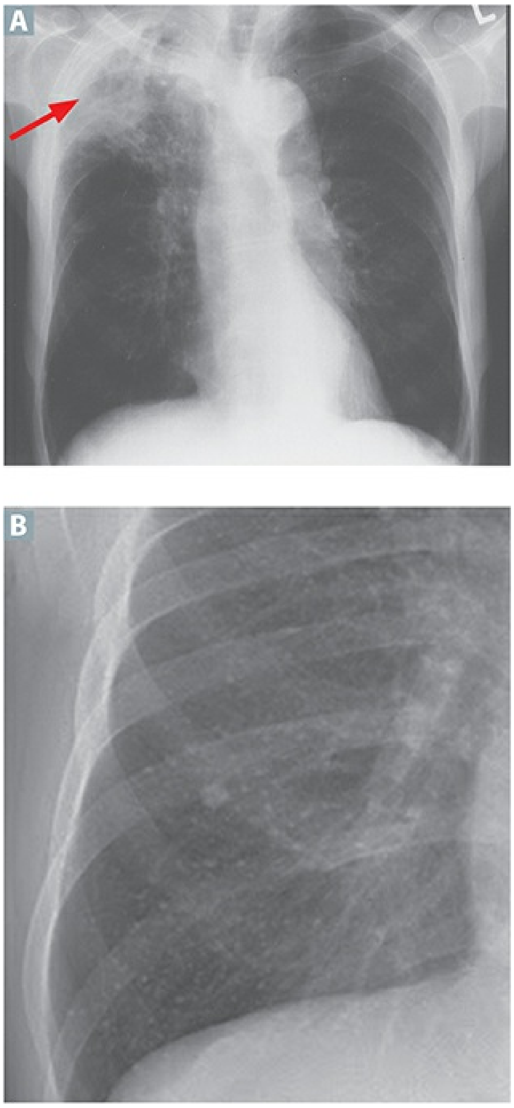


FIGURE 2.14-25. **Pulmonary TB. (A)** Right apical opacity with areas of cavitation *(arrow)* is seen in an older adult patient with reactivation TB. **(B)** Coned-in view of CXR in a young man with miliary TB shows innumerable 1- to 2-mm pulmonary nodules. (Image A reproduced with permission from Halter JB et al. Hazzard's *Geriatric Medicine and Gerontology*, 6th ed. New York, NY: McGraw-Hill; 2009. Image B reproduced with permission from USMLE-Rx.com.)

- Patients with HIV or those with primary TB may show lower lobe infiltrates with or without cavitation.
- Multiple fine nodular densities distributed throughout both lungs are typical of miliary TB, which represents hematologic or lymphatic dissemination.

Treatment

All cases (both latent and active) must be reported to local and state health departments. Respiratory isolation in a negative-pressure room should be instituted if active TB is suspected, and all healthcare workers in contact with the patient should wear N95 masks. Treatment measures are as follows:

- **Latent disease:** For a ⊕ PPD without signs or symptoms of active disease, treatment with rifampin for 4 months or with isoniazid (isonicotinic acid hydrazide [INH]) plus either rifampin or rifapentine for 3 months. Alternative regimens include INH for 6 months.
- **Active disease:** Directly observed multidrug therapy with a four-drug regimen (INH,

pyrazinamide, rifampin, ethambutol) for 2 months, followed by INH and rifampin for 4 months.

- **High-yield side effects of TB medications:**
  - Ethambutol can cause optic neuritis.
  - INH can cause hepatitis, peripheral neuropathy (consider administering pyridoxine concurrently to prevent this), and a lupus-like syndrome.
  - Pyrazinamide can lead to hyperuricemia or hepatitis.
  - Rifampin turns body fluids orange.

MNEMONIC

Patients with TB are RIPE for treatment—

Rifampin
Isoniazid
Pyrazinamide
Ethambutol

NONTUBERCULOUS MYCOBACTERIA

These organisms can cause a spectrum of disease, particularly in immunocompromised hosts.

- **Mycobacterium avium complex (MAC):** Can cause cavitary lung disease classically in older patients with underlying chronic lung disease (COPD, CF). Disseminated disease is classically seen in people with HIV and a $CD4^+$ cell count <50 µL. *Mycobacterium kansasii* can also cause cavitary lung disease under similar conditions.
- Other mycobacteria *(M marinum, M abscessus, M ulcerans, M chelonae)* can be isolated in chronic, nonhealing wounds.

Ubiquitous organisms cause pulmonary and disseminated infection in several demographic groups. The primary pulmonary form occurs in apparently healthy nonsmokers (Lady Windermere syndrome); a secondary pulmonary form affects patients with preexisting pulmonary disease such as COPD, TB, or CF. Disseminated infection occurs in AIDS patients with a $CD4^+$ cell count $<50/mm^3$ who are not on highly active antiretroviral therapy (HAART).

History/PE

- Disseminated *M. avium* infection in AIDS is associated with fever, weight loss, diarrhea, and severe anemia in patients who are not on HAART or chemoprophylaxis for MAC.

A

The next most appropriate step in management involves surgical debridement and amphotericin B. The patient has mucormycosis, a dangerous and aggressive infection found in patients who are diabetic and immunocompromised. Aggressive surgical debridement is warranted.

- Hepatosplenomegaly and lymphadenopathy are occasionally seen.
- Adrenal insufficiency is possible in the setting of adrenal infiltration.

Diagnosis

- The physician should obtain mycobacterial blood cultures (⊕ in 2–3 weeks).
- Labs show anemia, hypoalbuminemia, and ↑ serum alkaline phosphatase and LDH.
- Biopsy of lung, bone marrow, intestine, or liver reveals foamy macrophages with acid-fast bacilli (AFB). Typical granulomas may be absent in immunocompromised patients.

Treatment

Treat with macrolide (clarithromycin or azithromycin) + ethambutol ± rifabutin and consider HAART if the patient is drug-naive. Continue for >12 months and until CD4+ cell count $>100/mm^3$ for >6 months.

Prevention

Routine MAC prophylaxis is no longer recommended for HIV patients with CD4+ cell counts <50 and on HAART. Those not on HAART should receive chemoprophylaxis with azithromycin.

PNEUMOCYSTIS JIROVECII PNEUMONIA

Formerly known as *Pneumocystis carinii* pneumonia (PCP). Risk factors include impaired cellular immunity and AIDS.

History/PE

Presents with dyspnea on exertion, fever, nonproductive cough, tachypnea, weight loss, fatigue, and impaired oxygenation. Subacute (weeks) with AIDS. Acute respiratory failure with immunosuppressive therapy. Can also present as disseminated disease or as local disease in other organ systems. The differential diagnosis includes TB, viral pneumonia, histoplasmosis, and coccidioidomycosis.

Diagnosis

- Diagnosed by cytology of induced sputum or bronchoscopy specimen with silver stain and immunofluorescence (see Fig. 2.14-26A). Obtain an ABG to check PaO_2.

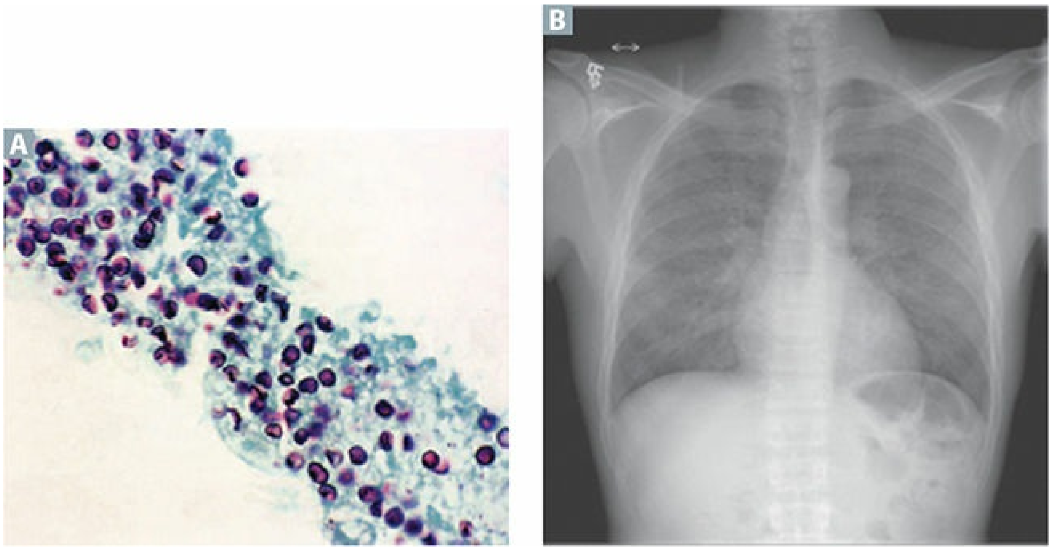


FIGURE 2.14-26. ***Pneumocystis* pneumonia. (A)** Lung tissue stained with silver uncovers folded

cysts containing comma-shaped spores. **(B)** Frontal CXR shows diffuse "ground-glass" lung opacities characteristic of PCP in this patient with AIDS and a CD4+ cell count of 26. (Image A reproduced with permission from Ryan KJ, Ray CG. *Sherris Medical Microbiology,* 5th ed. New York, NY: McGraw-Hill; 2010. Image B reproduced with permission from USMLE-Rx.com.)

- CXR most commonly shows diffuse, bilateral interstitial infiltrates with a ground-glass appearance (see Fig. 2.14-26B, "bat wing" or "butterfly" pattern), but any presentation is possible.
- ↑ β-d-Glucan and ↑ LDH can be useful but are nonspecific.

Treatment

The preferred regimen is high-dose TMP-SMX for 21 days, PO if mild to moderate, and IV if severe. Alternative regimens:

- **Mild to moderate:** trimethoprim + dapsone, or primaquine + clindamycin, or atovaquone
- **Severe:** pentamidine or primaquine + clindamycin

The physician should use a prednisone taper in patients with moderate to severe hypoxemia (Pa_{O_2} <70 mm Hg or an alveolar-arterial oxygen gradient ≥35).

KEY FACT

In patients with Pneumocystis pneumonia and moderate to severe hypoxemia (Pao_2 <70 mm Hg or an alveolar-arterial oxygen gradient ≥35), add a prednisone taper to ↓ lung inflammation and reduce mortality.

ANTHRAX

Caused by the spore-forming, gram ⊕ bacterium *Bacillus anthracis.* Infection is an occupational hazard for veterinarians; farmers; and individuals who handle animal wool, hair, hides, or bone meal products. Has been used as a biologic weapon. *B anthracis* can cause cutaneous (most common), inhalation (most deadly), or GI anthrax. There is no person-to-person spread of anthrax.

History/PE

- **Cutaneous:** Presents 1 to 7 days after skin exposure and penetration of spores. The lesion begins as a pruritic papule that enlarges to form an ulcer surrounded by a satellite bulbus/lesion with an edematous halo and a round, regular, raised edge. Regional lymphadenopathy is also characteristic. The lesion evolves into a black eschar within 7 to 10 days (see Fig. 2.14-27).

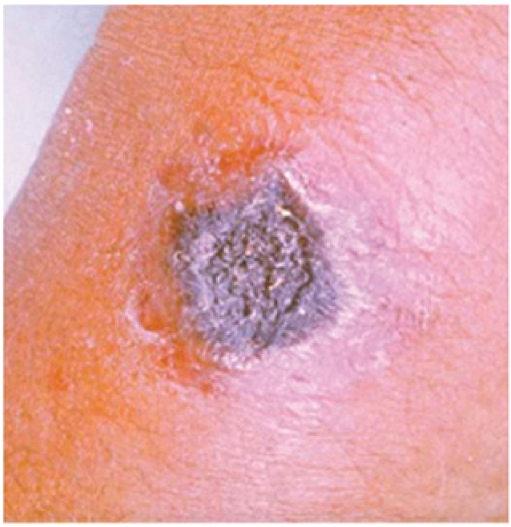


FIGURE 2.14-27. **Cutaneous anthrax.** Black eschar is seen on the forearm. (Reproduced courtesy of James H. Steele, Centers for Disease Control and Prevention, Atlanta, GA.)

- **Inhalational:** Presents with fever, dyspnea, hypoxia, hypotension, or symptoms of pneumonia (1–3 days after exposure), classically caused by hemorrhagic mediastinitis. Patients typically do not have pulmonary infiltrates.
- **GI:** Occurs after the ingestion of poorly cooked, contaminated meat. It can present with dysphagia, nausea/vomiting, bloody diarrhea, and abdominal pain.

Diagnosis

Criteria for diagnosis include culture isolation or two nonculture supportive tests (PCR, immunohistochemical staining, or enzyme-linked immunosorbent assay [ELISA]). CXR is the most sensitive test for inhalational disease (shows a widened mediastinum and pleural effusions).

Treatment

- **Best initial treatment:** Ciprofloxacin or doxycycline plus one to two additional antibiotics for at least 14 days for inhalational disease or cutaneous disease of the face, head, or neck.
- For other cutaneous disease, treat for 7 to 10 days. Postexposure prophylaxis (ciprofloxacin) to prevent inhalation anthrax should be continued for 60 days.

ACUTE PHARYNGITIS

Viral causes are more common (90% in adults), but it is important to identify streptococcal pharyngitis (group A β-hemolytic *Streptococcus pyogenes*). Etiologies are as follows:

- **Bacterial:** Group A *Streptococcus* (GAS), *Neisseria gonorrhoeae, Corynebacterium diphtheriae, M pneumoniae*
- **Viral:** Rhinovirus, coronavirus, adenovirus, herpes simplex virus (HSV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), influenza virus, coxsackievirus, acute HIV infection

KEY FACT

Early antibiotic treatment of streptococcal pharyngitis can prevent rheumatic fever but not glomerulonephritis.

History/PE

- **Typical of streptococcal pharyngitis:** Fever, sore throat, pharyngeal erythema (see Fig. 2.14-28), tonsillar exudate, cervical lymphadenopathy, soft palate petechiae, headache, vomiting, scarlatiniform rash (indicates scarlet fever)

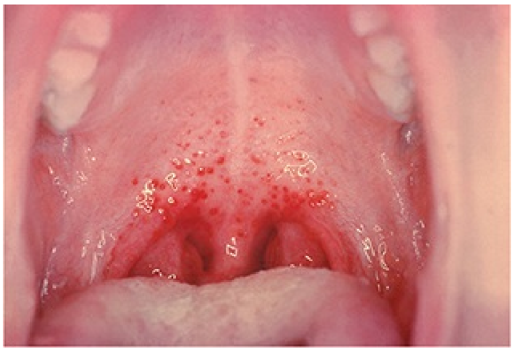


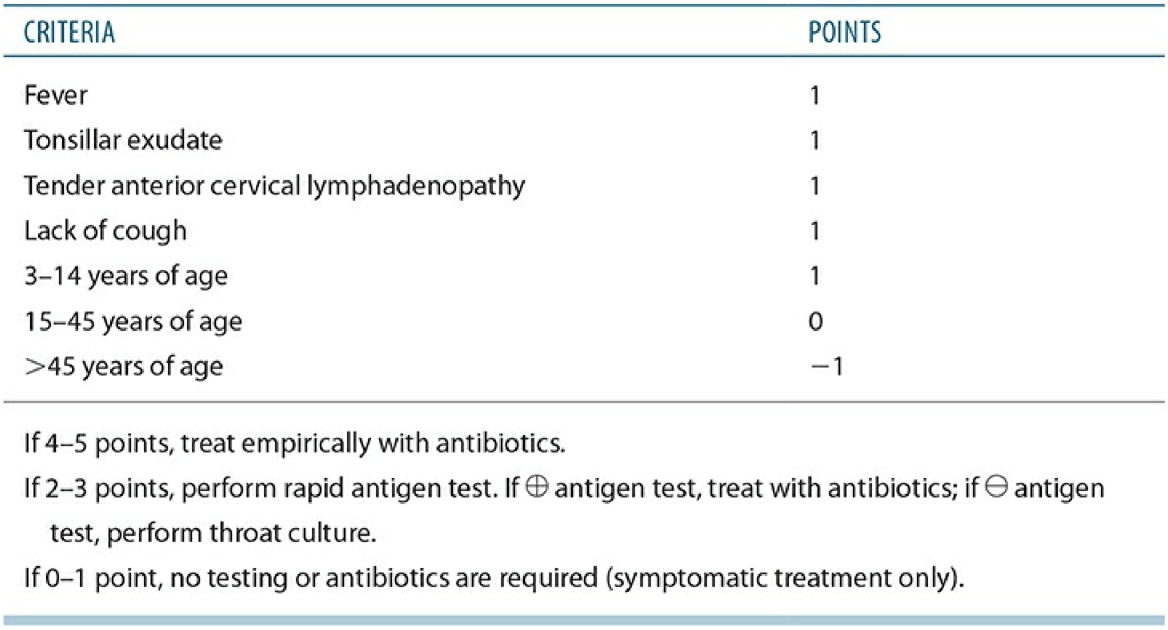
FIGURE 2.14-28. **Pharyngeal erythema with palatal petechiae.** *Streptococcus pyogenes* is the most common bacterial cause of pharyngitis. (Reproduced courtesy of Dr. Heinz F. Eichenwald from the Centers for Disease Control and Prevention, Atlanta, GA.)

- **Atypical of streptococcal pharyngitis:** Coryza, hoarseness, rhinorrhea, cough, conjunctivitis, anterior stomatitis, ulcerative lesions, GI symptoms

Diagnosis

Diagnosed by clinical evaluation, rapid GAS antigen detection, and throat culture. If three out of four Centor criteria are met (see Table 2.14-19), the sensitivity of rapid antigen testing is >90%.

TABLE 2.14-19. **Modified Centor Criteria (Centor Criteria + Age)**



CRITERIA	POINTS
Fever	1
Tonsillar exudate	1
Tender anterior cervical lymphadenopathy	1
Lack of cough	1
3–14 years of age	1
15–45 years of age	0
>45 years of age	−1

If 4–5 points, treat empirically with antibiotics.

If 2–3 points, perform rapid antigen test. If ⊕ antigen test, treat with antibiotics; if ⊖ antigen test, perform throat culture.

If 0–1 point, no testing or antibiotics are required (symptomatic treatment only).

Treatment

If GAS is suspected, begin empiric antibiotic therapy with penicillin for 10 days.

Cephalosporins, amoxicillin, and azithromycin are alternative options. Symptom relief can be attained with fluids, rest, antipyretics, and saltwater gargles.

Complications

- **Nonsuppurative:** Acute rheumatic fever, poststreptococcal glomerulonephritis
- **Suppurative:** Cervical lymphadenitis, mastoiditis, sinusitis, otitis media, retropharyngeal or peritonsillar abscess, and, rarely, thrombophlebitis of the jugular vein (Lemierre syndrome) caused by *Fusobacterium*, an oral anaerobe
- Peritonsillar abscess may present with odynophagia, trismus (“lockjaw”), a muffled “hot potato” voice, unilateral tonsillar enlargement, and erythema, with the uvula and soft palate deviated away from the affected side; culture abscess fluid and localize the abscess via intraoral ultrasound or CT; treat with antibiotics and surgical drainage

KEY FACT

Acute necrotizing mediastinitis is a life-threatening complication of untreated retropharyngeal abscess that presents with fever, chest pain, and dyspnea. It requires urgent surgical drainage to prevent spread to the posterior mediastinum, which may cause lethal pleural and pericardial effusions.

KEY FACT

All patients with a history of rheumatic fever should be given routine penicillin prophylaxis to prevent recurrent group A *Streptococcus* infection.

ORAL INFECTIONS

LUDWIG ANGINA

Rapidly progressive cellulitis of the submandibular space that may cause airway compromise from rapidly expanding edema. Usually caused by polymicrobial infection in the setting of poor oral hygiene. IV broad-spectrum antibiotics and diligent airway management are necessary; surgical drainage is performed if there is abscess formation (uncommon).

ACUTE LYMPHADENITIS

Unilateral and rapid onset (<1 week), commonly caused by *S aureus* and *S pyogenes*, typically involving the submandibular lymph nodes. Antibiotics are required if symptoms (fluctuance, fever, cellulitis) are present to prevent abscess formation.

SINUSITIS

Refers to inflammation of the paranasal sinuses. The maxillary sinuses are most commonly affected. Subtypes include the following:

- **Acute sinusitis (symptoms lasting <1 month):** Most commonly associated with viruses, *S pneumoniae, H influenzae,* and *M catarrhalis.* Bacterial causes are rare and characterized by purulent nasal discharge, facial or tooth tenderness, hyposmia/anosmia, and symptoms lasting >10 days.

- **Chronic sinusitis (symptoms persisting >3 months):** A chronic inflammatory process often caused by obstruction of sinus drainage and ongoing low-grade anaerobic infections.

KEY FACT

Potential complications of sinusitis include meningitis, frontal bone osteomyelitis, cavernous sinus thrombosis, and abscess formation.

KEY FACT

Ludwig angina is a bilateral cellulitis of the submental, submaxillary, and sublingual spaces that usually results from an infected tooth. It presents with dysphagia; drooling; fever; and a red, warm mouth, and it can lead to death from asphyxiation.

History/PE

- Presents with fever, facial pain/pressure, headache, nasal congestion, and discharge. Examination may reveal tenderness, erythema, and swelling over the affected area.
- High fever, leukocytosis, and a purulent nasal discharge are suggestive of acute bacterial sinusitis.

KEY FACT

Beware of invasive and life-threatening fungal sinusitis (caused by *Mucor* and *Rhizopus*) in patients with poorly controlled diabetes mellitus, immune compromise, or neutropenia.

Diagnosis

- A clinical diagnosis. Culture and imaging are generally not required for acute sinusitis but may guide the management of chronic cases.
- Transillumination shows opacification of the sinuses (low sensitivity).
- CT is the test of choice for sinus imaging (see Fig. 2.14-29) but is usually necessary only if symptoms persist after treatment.

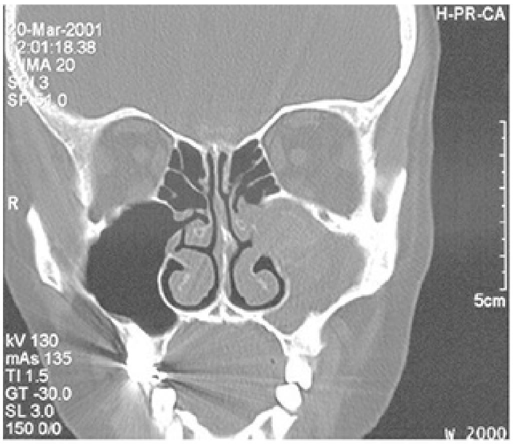


FIGURE 2.14-29. Sinusitis. Coronal CT image shows an opacified left maxillary sinus and marked associated bony thickening, consistent with chronic maxillary sinusitis. (Reproduced with permission from Lalwani AK. *Current Diagnosis & Treatment in Otolaryngology—Head and Neck Surgery*, 2nd ed. New York, NY: McGraw-Hill; 2008.)

Treatment

Most cases of acute sinusitis are viral and/or self-limited and are treated with symptomatic therapy (decongestants, antihistamines, nasal saline lavage, pain relief).

- **Acute bacterial sinusitis:** The physician should consider either amoxicillin/clavulanate for 10 days or clarithromycin, azithromycin, trimethoprim-sulfamethoxazole (TMP-SMX), a fluoroquinolone, or a second-generation cephalosporin for 10 days.
- **Chronic sinusitis:**
  - Antibiotics like those used for acute disease may be prescribed for chronic sinusitis, although a longer course (3–6 weeks) may be necessary.
  - Adjuvant therapy with intranasal corticosteroids, decongestants, and/or antihistamines may be useful in combating the allergic/inflammatory component of the disease.
  - Surgical intervention may be required.

HEMOPTYSIS

Hemoptysis is the expectoration of blood from the lower respiratory tract, below the vocal cords, which can be caused by various etiologies. These etiologies can be divided into life-threatening and non-life-threatening hemoptysis. Bleeding from the pulmonary arteries (low-pressure system) is commonly non-life-threatening, whereas bleeding from the bronchial arteries (high-pressure system) may be life-threatening. Hemoptysis is often classified as mild (<30 mL), moderate (31–100 mL), severe (100–600 mL), or massive. Massive hemoptysis is defined by a number of criteria, often ranging from 100 mL to more than 600 mL over 24 hours with respiratory or hemodynamic compromise.

Etiologies of hemoptysis: Airway disease (bronchitis, bronchiectasis, bronchial neoplasm, foreign bodies), pulmonary parenchymal disease (infection such as TB, rheumatic and immune disorders such as vasculitis, connective tissue disorders such as Ehlers-Danlos syndrome), pulmonary vascular disorders (elevated pulmonary capillary pressure, pulmonary arteriovenous malformation, pulmonary embolism), and bleeding disorders.

History/PE

Assess for risk factors for specific diseases such as lung cancer in patients with heavy smoking history. Rule out life-threatening hemoptysis, and observe for airway compromise.

Diagnosis

- Order CXR first and consider CT imaging of the chest if needed to rule out specific etiologies.
- CBC, coagulation studies, urinalysis, rheumatologic workup should be performed as needed.

Treatment

- In the case of impending airway compromise due to massive hemoptysis, secure the airway by placing an endotracheal tube while evaluating the cause.
- Management of hemoptysis includes hemodynamic stabilization and treatment of the

underlying cause. In the case of persistent bleeding, bronchoscopic interventions and embolization can be performed to control the bleeding (Fig. 2.14-30).

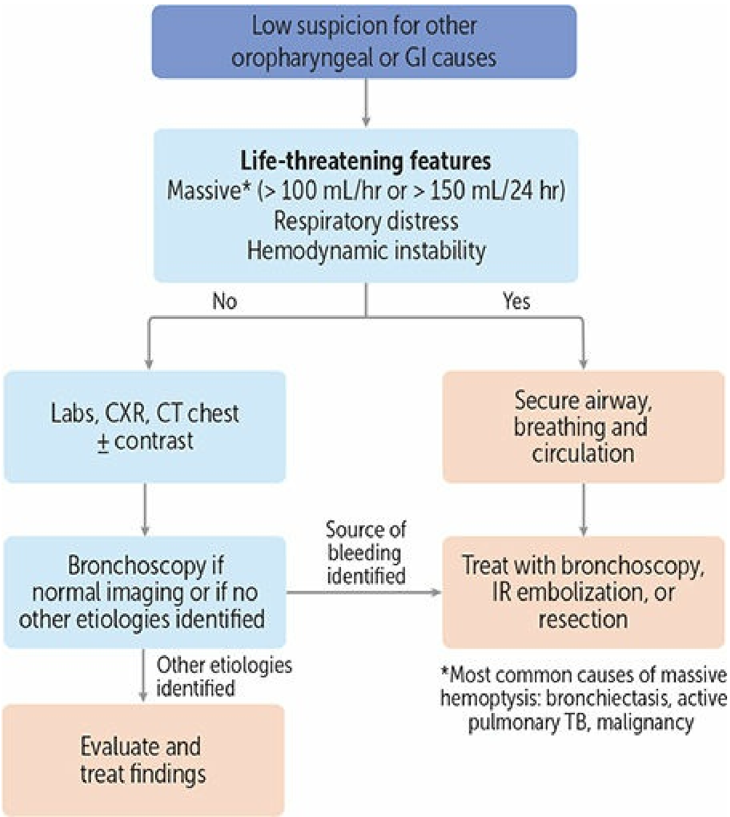

Low suspicion for other oropharyngeal or GI causes
Life-threatening features
Massive* (> 100 mL/hr or > 150 mL/24 hr)
Respiratory distress
Hemodynamic instability
No
Yes
Labs, CXR, CT chest ± contrast
Secure airway, breathing and circulation
Bronchoscopy if normal imaging or if no other etiologies identified
Source of bleeding identified
Treat with bronchoscopy, IR embolization, or resection
Other etiologies identified
Evaluate and treat findings
*Most common causes of massive hemoptysis: bronchiectasis, active pulmonary TB, malignancy

FIGURE 2.14-30. **Evaluation of hemoptysis.** (Reproduced with permission from USMLE-Rx.com.)

PLEURAL DISEASE

PLEURAL EFFUSION

An abnormal accumulation of fluid in the pleural space. Classified as follows:

- **Transudate:** Secondary to ↑ pulmonary capillary wedge pressure (PCWP) or ↓ oncotic pressure
- **Exudate:** Secondary to ↑ pleural vascular permeability

See Figure 2.14-31 for an algorithm showing etiology of pleural effusion. Table 2.14-20 lists the possible causes of both transudates and exudates.

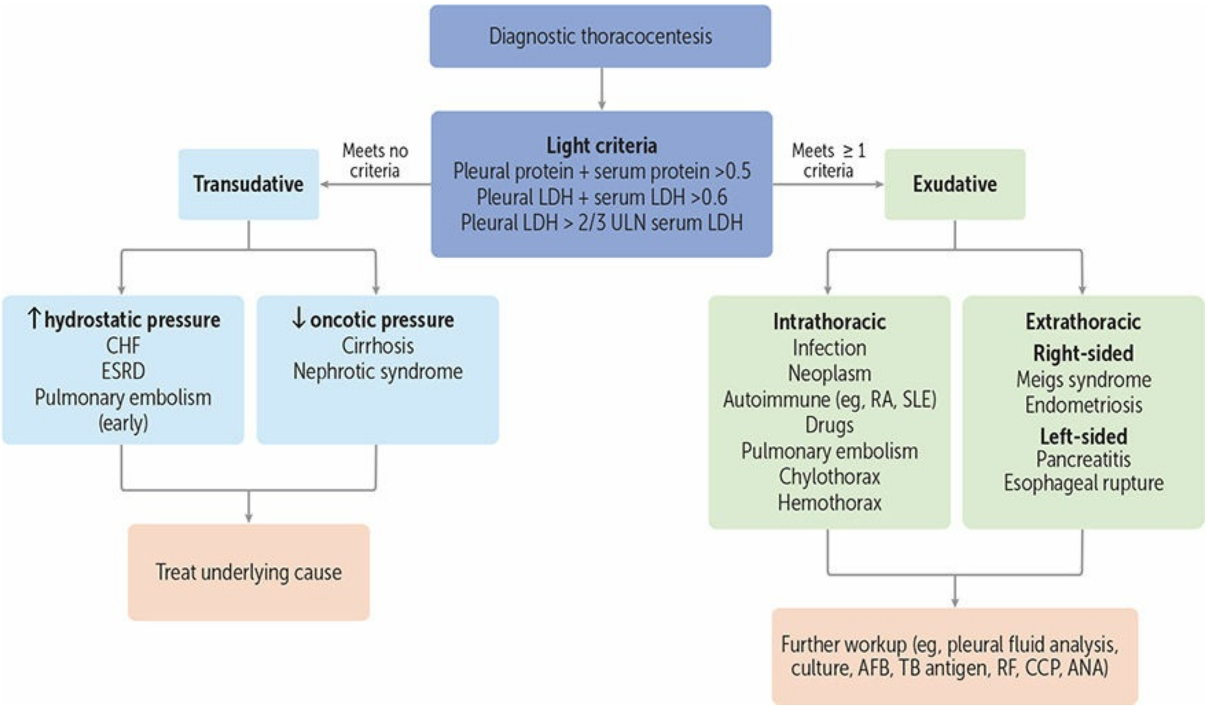

Diagnostic thoracocentesis
Light criteria
Pleural protein + serum protein >0.5
Pleural LDH + serum LDH >0.6
Pleural LDH > 2/3 ULN serum LDH
Meets no criteria
Meets ≥ 1 criteria
Transudative
Exudative
↑ hydrostatic pressure
CHF
ESRD
Pulmonary embolism (early)
↓ oncotic pressure
Cirrhosis
Nephrotic syndrome
Treat underlying cause
Intrathoracic
Infection
Neoplasm
Autoimmune (eg, RA, SLE)
Drugs
Pulmonary embolism
Chylothorax
Hemothorax
Extrathoracic
Right-sided
Meigs syndrome
Endometriosis
Left-sided
Pancreatitis
Esophageal rupture
Further workup (eg, pleural fluid analysis, culture, AFB, TB antigen, RF, CCP, ANA)

FIGURE 2.14-31. **Etiology of pleural effusion based on pleural fluid analysis.** (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.14-20. **Causes of Pleural Effusions**

TRANSUDATES	EXUDATES
Congestive heart failure	Pneumonia (parapneumonic effusion)
Cirrhosis (hepatic hydrothorax)	TB
Nephrotic syndrome	Malignancy
	Pulmonary embolism
	Collagen vascular disease (SLE)
	Pancreatitis
	Trauma
	Chylothorax (triglycerides)

History/PE

Presents with dyspnea, pleuritic chest pain, and/or cough. Exam reveals dullness to percussion and ↓ breath sounds over the effusion (see Table 2.14-21). A pleural friction rub may be present.

TABLE 2.14-21. **Pulmonary Physical Exam Findings**

	LUNG CONSOLIDATION (eg, LOBAR PNEUMONIA)	PLEURAL EFFUSION	PNEUMOTHORAX
Percussion	Dull	Dull	Hyperresonant
Tactile fremitus	↑	↓	↓
Breath sounds	Bronchial	↓	↓/Absent
Voice transmission	Bronchophony Egophony	↓	↓
Crackles	Present (often)	Absent	Absent

Diagnosis

- **Best initial test:** CXR, blunting of the costophrenic angle. Lateral decubitus view is most sensitive; it also is used to assess for loculation.
- **Next step:** Thoracentesis. It is indicated for new effusions >1 cm in the decubitus view, except with bilateral effusions and other clinical evidence of CHF.
- Using Light criteria can determine if the effusion is transudative or exudative (see Table 2.14-22).

TABLE 2.14-22. **Light Criteria for Pleural Effusions**[a]

MEASURE	VALUE
Pleural protein/ serum protein	>0.5
Pleural LDH/ serum LDH	>0.6
Pleural fluid LDH	More than 2/3 of the ULN serum LDH

[a] An effusion is an exudate if any of the previous criteria are met.

  - Transudative effusions: Typically have a pH of 7.4 to 7.55
  - Exudative effusions: Typically have a pH of pH <7.4
- Effusion is an exudate if it meets any Light criteria.
  - Exudative effusions: Require further workup (eg, pleural fluid glucose, amylase, cytology, cell count, culture, Gram stain, AFB, TB antigen, RF, CCP, ANA)
- **Complications:**
  - Parapneumonic effusion and empyema: Pleural effusions that arise as result of pneumonia, lung abscess, or bronchiectasis; see Table 2.14-23

TABLE 2.14-23. **Parapneumonic Effusions and Empyemas**

	UNCOMPLICATED PARAPNEUMONIC EFFUSION	COMPLICATED PARAPNEUMONIC EFFUSION	EMPYEMA
Etiology	Fluid movement into pleural space (caused by inflammation associated with pneumonia)	Persistent bacterial invasion into pleural space	Bacterial colonization of pleural space
Appearance	Clear/cloudy	Cloudy	Purulent
Pleural fluid analysis	pH >7.2 Glucose: Normal/↓ LDH ratio >0.6	pH <7.2 Glucose: ↓ LDH ratio >0.6	pH <7.2 Glucose: ↓ LDH ratio >0.6
Pleural fluid Gram stain and culture	Negative	Negative	Positive
Treatment	Antibiotics	Antibiotics Chest tube	Antibiotics Chest tube

  - Recurrent effusion

Treatment

- Treat the underlying cause of the effusion.
- See Table 2.14-23 for treatment of parapneumonic effusions and empyemas.
- **Recurrent effusions:** May require pleurodesis (procedure to obliterate pleural space).

KEY FACT

Complicated parapneumonic effusions necessitate chest tube drainage.

PNEUMOTHORAX

Collection of air in the pleural space that can lead to pulmonary collapse. Etiologies are the following:

- **Primary spontaneous pneumothorax:** Due to rupture of subpleural apical blebs (usually found in tall, thin, young males).
- **Secondary pneumothorax:** Due to COPD, trauma, infections (TB, *P jirovecii*), and iatrogenic factors (thoracentesis, subclavian line placement, positive-pressure mechanical ventilation, bronchoscopy with biopsy).
- **Tension pneumothorax:** A pulmonary or chest wall defect acts as a one-way valve, causing air trapping in the pleural space. Buildup of air pushes the mediastinum to the opposite side of the chest, which can obstruct venous return to the heart, leading to hemodynamic instability and even cardiac arrest unless immediately treated.

MNEMONIC

Presentation of pneumothorax—

P-THORAX

Pleuritic pain
Tracheal deviation

Hyperresonance
Onset sudden
Reduced breath sounds (and dyspnea)
Absent fremitus (asymmetric chest wall)
X-ray showing collapse

History/PE

- Pneumothorax presents with acute onset of unilateral pleuritic chest pain and dyspnea.
- Examination reveals tachypnea, diminished or absent breath sounds, hyperresonance, ↓ tactile fremitus, and JVD secondary to compression of the SVC.
- **Tension pneumothorax:** Presents with respiratory distress, hypoxia, tracheal deviation, and hemodynamic instability.

Diagnosis

- The diagnosis of a tension pneumothorax should be made clinically.
- CXR shows the presence of a visceral pleural line and/or lung retraction from the chest wall (best seen in end-expiratory films; see Fig. 2.14-32). In an emergency department (ED) or ICU setting, bedside ultrasound can be used, and it has high sensitivity and specificity.

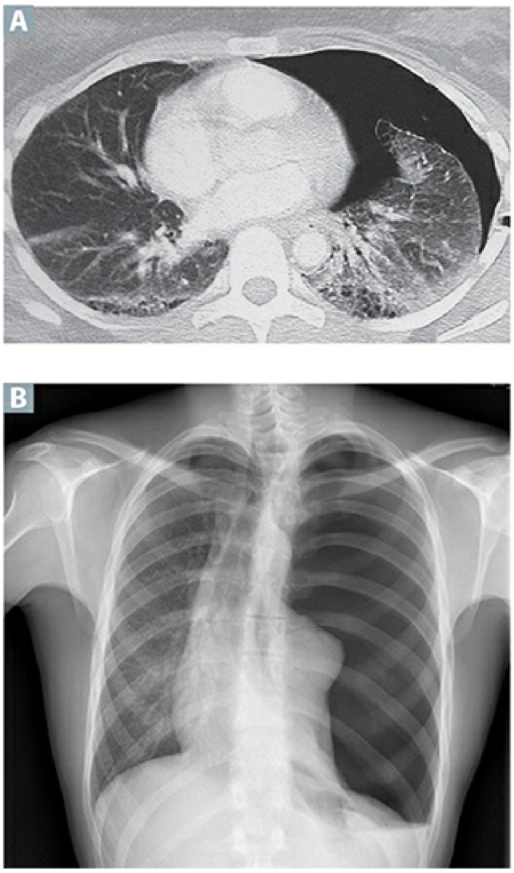


FIGURE 2.14-32. **Pneumothorax. (A)** Pneumothorax. CT shows collapsed left lung. **(B)** Tension pneumothorax. (Image A reproduced with permission from Miura K, Kondo R, Kurai M, et al. Birt-Hogg-Dubé syndrome detected incidentally by asymptomatic bilateral pneumothorax in health screening: a case of a young Japanese woman. *Surg Case Rep.* 2015;1:17. doi:10.1186/s40792-015-0014-8. Image B reproduced with permission from Rosat A, Díaz C. Reexpansion pulmonary edema after drainage of tension pneumothorax. *Pan Afr Med J.* 2015;22:143. doi:10.11604/pamj.2015.22.143.8097.

KEY FACT

Treatment of a tension pneumothorax requires needle decompression first and then chest tube placement.

Treatment

- **Tension pneumothorax:** Requires immediate needle decompression (second intercostal space at the midclavicular line) followed by chest tube placement.
- **Small pneumothorax (≤2 cm):** Observation ± supplemental O_2. It may resorb spontaneously.
- **Large (>3 cm), symptomatic pneumothorax:** Needle aspiration or small-bore chest tube placement.
- **Patients who are unstable or who have recurrent pneumothorax:** Chest tube placement.

PULMONARY SLEEP DISORDERS

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (OSA) is a sleep disorder characterized by transient obstruction of the upper airway that causes hypoxemia. Etiology may be central (eg, stroke), secondary (eg, obesity), or mixed. Risk factors include male sex, older age, obesity, craniofacial abnormalities, upper airway abnormalities (adenotonsillar hypertrophy [children]), sedative use (eg, alcohol, benzodiazepines), smoking, and many others.

History/PE

Cardinal features:

- **Irregular respiratory pattern during sleep:** Obstructive apneas, hypopneas, or respiratory effort–related arousals (RERAs)
- **Daytime symptoms related to poor sleep:** Somnolence, fatigue, poor concentration, morning headaches
- **Signs of disturbed sleep:** Snoring, gasping, choking, restlessness

KEY FACT

The **STOP-BANG survey** is a clinical questionnaire that can be used to assess the risk of OSA and direct further sleep testing: **S**noring, **T**iredness, **O**bserved stop in breathing, increased blood **P**ressure, **B**ody mass index (BMI) >35 kg/m^2, **A**ge >50 years, **N**eck circumference >40 cm, male **G**ender. The presence of ≥3 positive items should prompt sleep testing.

Complications:

- ↑ cardiovascular morbidity (systemic hypertension, PAH, coronary artery disease, arrhythmias, heart failure, polycythemia, and stroke)
- ↑ risk for insulin resistance and type 2 diabetes mellitus
- ↑ risk for motor vehicle collisions caused by impaired alertness

Diagnosis

- **Best initial test:** Polysomnography (sleep study) based on apnea-hypopnea index ([AHI] = apneas + hypopneas/total hours of sleep) and presence or absence of related symptoms
- Diagnosis is confirmed with the following:
  - AHI ≥5 PLUS symptoms
  - AHI ≥15 regardless of symptoms

Treatment

- **Best initial therapy:** Weight loss (if applicable) and CPAP
- **Alternatives:** Oral appliances, hypoglossal nerve stimulation, and maxillomandibular advancement (bones of upper and lower jaw surgically repositioned to relieve obstruction)
- **Last resort:** Tracheostomy

OBESITY HYPOVENTILATION SYNDROME

Obesity hypoventilation syndrome (OHS) is a sleep disorder defined as awake alveolar hypoventilation in an obese individual that cannot be attributed to other conditions associated with alveolar hypoventilation.

History/PE

Presents with hypersomnolence and obesity. OHS is further characterized by coexisting sleep disturbances:

- **OHS with OSA (90% of patients):** Presents with symptoms of OSA (see earlier section)
- **OHS with sleep-related hypoventilation (10%):** Presents the same as OHS + OSA but witnessed apneas during sleep are uncommon

Diagnosis

Diagnosis of exclusion. Patient must meet all of the following criteria:

- Obesity (body mass index [BMI] >30 kg/m^2)
- Awake alveolar hypoventilation ($Paco_2$ >45 mm Hg)
- Exclusion of alternative causes of hypercapnia and hypoventilation

Treatment

- **Best initial treatment:** Weight loss and noninvasive positive airway pressure (PAP)
  - **OHS + OSA:** CPAP
  - Initiate bilevel positive airway pressure (BiPAP) if initial management with CPAP fails
  - **OHS + hypoventilation:** BiPAP
- **Next best treatment:**
  - Bariatric surgery
  - Tracheostomy (last resort)

NOSE AND THROAT

RHINITIS

Rhinitis is characterized by symptoms of rhinorrhea (posterior or anterior), nasal congestion, sneezing, and itching. Although most forms of rhinitis involve inflammation, some forms, such as vasomotor rhinitis, do not. It may be further classified into allergic and nonallergic causes.

Allergic Rhinitis

Pathogenesis

- Results from IgE-mediated type 1 hypersensitivity reaction of the nasal mucosa
- Commonly associated with atopic diseases such as asthma and eczema

History/PE

Presents with rhinitis in response to allergens. Based on temporal pattern, can be further classified as follows:

- **Intermittent/seasonal:** Allergic reactions to grass/trees or pollen (hay fever); occurs in late spring/summer
- **Persistent/perennial:** Allergic reactions to house dust, dust mites, molds, dogs, cats
- **Food allergens:** May also be contributory; however, evidence is lacking

Diagnosis

- Clinical diagnosis based on typical history and nasal examination
- Skin prick test involves introducing common allergens into the skin to observe for hypersensitivity reactions; this can help identify allergens
- Serum total IgE is generally increased
- Serum radio-allergosorbent test (RAST) is a blood test that identifies IgE antibodies to specific allergens

Treatment

- Allergen avoidance
- **Medications:**
  - Second-generation oral nonsedating antihistamines such as loratadine, cetirizine, and fexofenadine
  - Intranasal steroids such as fluticasone, beclomethasone, or mometasone nasal sprays titrated to minimum effective dose; sometimes these internal steroids may be combined with intranasal antihistamines
  - Leukotriene antagonists such as montelukast; this is also beneficial with concomitant asthma
- **Immunotherapy:** Allergen exposure and desensitization

Nonallergic Rhinitis

Nonallergic rhinitis is a subtype of rhinitis without an allergic or infectious cause. It accounts for up to 50% of cases of rhinitis in adults.

Etiology/Pathogenesis

- **Irritants:** Cigarette smoke (tobacco), pollutants, occupational (chemicals such as cleaning products)
- **Vasomotor:** Caused by increased blood flow to the nasal mucosa; it is instigated by temperature changes or dry air and irritant odors
- **Gustatory:** Clear rhinorrhea after ingestion of food (most often spicy)
- **Drug induced:** Due to antihypertensives, NSAIDs, PDE-5 inhibitors, or cocaine

- **Hormonal rhinitis:** Onset during pregnancy; it resolves with end of pregnancy
- **Senile rhinitis** (also called atrophic rhinitis): occurs in older adults when the nasal glands that produce moisture fail to function adequately

Diagnosis

Workup to exclude allergic rhinitis (see earlier information).

Treatment

- Treatment is symptom driven.
- The patient should avoid any precipitating factors.
- Intranasal corticosteroids (eg, fluticasone) and intranasal antihistamines (eg, azelastine) alone or in combination treat nasal congestion, postnasal drip, rhinorrhea, and sneezing.
- Intranasal anticholinergics (eg, ipratropium) treat rhinorrhea. Decongestants (eg, phenylephrine, oxymetazoline) help with nasal congestion.
- Nasal irrigation and intranasal capsaicin may help.

NASAL POLYPS

Nasal polyps are benign outgrowths of nasal mucosa, and they represent the most common tumors of the nasal cavity. They commonly occur in association with allergic rhinitis, acute and chronic infections, and CF.

History/PE

- Patients present with nasal obstruction, postnasal discharge, congestion, sneezing, rhinorrhea, hyposmia, and anosmia.
- Important associations:
  - Aspirin allergy
  - Sinus infections
  - Asthma

Diagnosis

- Coronal sinus CT scanning is first-line imaging modality.
- Endoscopy can sometimes be helpful for evaluation in the clinic.
- Nasal masses that do not appear typical or respond to treatment should be biopsied.

Treatment

- **Medical treatment:**
  - Oral corticosteroids are the most effective.
  - Intranasal corticosteroids (mometasone, beclomethasone) are less effective. Other medical options include leukotriene antagonists (montelukast) or IL inhibitors (dupilumab).
- Surgical removal is indicated in select cases due to severe symptoms of obstruction or infection refractory to medical treatment.
- The physician should concomitantly treat predisposing factors (eg, underlying allergy).

EPISTAXIS

Epistaxis (bleeding from the nose) may either be anterior or posterior, based on the location of bleeding.

- **Anterior epistaxis:** This is the most common (90%) and tends to be self-limited. Bleeding is most often from the Kiesselbach plexus (eg, the area of anastomosis of the septal branch of the anterior ethmoidal artery, the lateral nasal branch of the sphenopalatine artery, and the septal branch of the superior labial branch of the facial artery).
- **Posterior epistaxis:** This is less common (10%) and may result in significant hemorrhage. Bleeding occurs from the posterolateral branches of the sphenopalatine artery and, rarely, the carotid artery.

Etiology

Local causes of epistaxis include mucosal irritation (eg, nose picking, dry air, rhinitis, foreign body), facial trauma, intranasal drugs (cocaine, intranasal corticosteroids), or tumors (nasopharyngeal carcinomas).

Systemic conditions or drugs may also cause epistaxis (eg, anticoagulation, antiplatelet medications, alcohol, bleeding disorders [eg, von Willebrand disease], vascular malformations [nasal hemangioma], or hypertension).

Treatment

Figure 2.14-33 outlines the approach to the management of epistaxis.

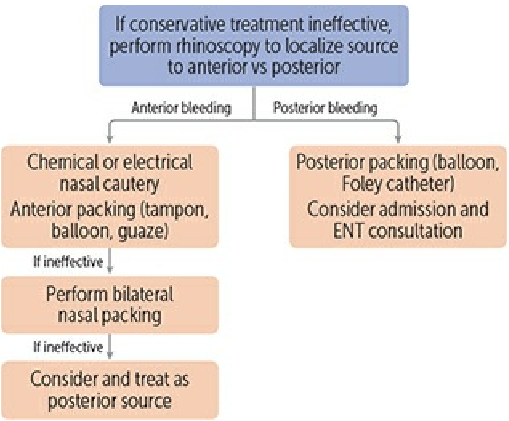

If conservative treatment ineffective, perform rhinoscopy to localize source to anterior vs posterior
Anterior bleeding
Posterior bleeding
Chemical or electrical nasal cautery
Anterior packing (tampon, balloon, guaze)
Posterior packing (balloon, Foley catheter)
Consider admission and ENT consultation
If ineffective
Perform bilateral nasal packing
If ineffective
Consider and treat as posterior source

FIGURE 2.14-33. Approach to treatment of active nosebleed. (Reproduced with permission from USMLE-Rx.com.)

- **Initial assessment and resuscitation:**
  - Assess and treat for airway, breathing, and cardiovascular (fluid resuscitation, redundant large-bore IV lines as indicated) compromise.
  - Target history to rule out conditions that predispose to bleeding (detailed earlier).
  - Laboratory tests: Coagulation studies (for anticoagulated patients, CBC, type and cross).
- **Initial conservative treatment:**
  - Position patient: Elevate body and bend forward.
  - Administer topical vasoconstrictor (eg, oxymetazoline) and local anesthetic (lidocaine) and pinch nostrils for 10 to 15 minutes.
  - Apply cold compress.
  - If conservative measures fail, examine nose to look for sources of bleeding (rhinoscopy, speculum).
- **Subsequent treatment of anterior bleeding:**
  - **Cauterization:** This is considered first line; either chemical (silver nitrate) or electrical

  cautery is possible.
  - **Nasal packing:** Nasal tampons, ribbon gauze, or nasal balloon catheters can be used; if unilateral packing ineffective, bilateral nasal packing can be performed.

KEY FACT

Brisk bleeding even after adequate nasal packing may indicate a posterior source of bleeding.

- **Subsequent treatment of posterior bleeding:**
  - Balloon catheter is preferred; alternatively, a Foley catheter can be used.
  - These patients may require hospitalization and urgent ear, nose, and throat (ENT) consultation.

Complications

Prolonged retention of nasal packing (>72 hours) increases the risk of complications, including necrosis, toxic shock syndrome, sinus or nasolacrimal infections, and dislodgment.

KEY FACT

Consider toxic shock syndrome in a patient with fever, hypotension, desquamation, and mucosal hyperemia after receiving nasal packing.

ADENOTONSILLAR HYPERTROPHY

Adenoids develop at the posterior surface of the nasopharynx and grow to a final size at 6 to 7 years of age. Palatine tonsils are located toward the end of the soft palate. Both structures are dense in B and T lymphocytes and play a role in local immunity and in host immune defense. Adenotonsillar hypertrophy is characterized by recurrent infections and hypertrophy of the lymphoid-rich structures.

History/PE

Adenotonsillar hypertrophy usually manifests in children as recurrent infections and sleep-disordered breathing (SDB).

- **Adenoid hypertrophy:** History of mouth breathing, hyponasal voice, adenoid facies, rhinorrhea, and postnasal drip is commonly described.
- **Tonsillar hypertrophy**: History of recurrent infections (most commonly viral and then bacterial) and airway and feeding difficulties, such as dysphagia and SDB with OSA. Voice changes and dental malocclusion may be seen.
- **SDB:** History of excessive daytime somnolence, failure to thrive, enuresis, poor school performance, and/or behavioral disturbance due to chronic sleep deprivation.

Diagnosis

- **Adenoid hypertrophy:** Rule out other causes of snoring and SDB such as anterior nasal obstruction.
  - **Best diagnostic test:** Nasopharyngoscopy to visualize the hypertrophied adenoid tissue
  - **Other:** Lateral x-ray of the neck to visualize the adenoids

- **Tonsillar hypertrophy:** Tonsil grading by physical exam is informative.
- **SDB:** Best diagnostic test: Polysomnography.

Treatment

- Infections should be first treated with supportive treatment as needed (pain control, adequate fluid intake, antibacterial if streptococcal infection is suspected).
- Use modified Centor criteria to decide on the use of antibiotics against *S pyogenes* (most common bacterial pathogen): Absence of cough, swollen/tender anterior cervical lymph nodes, temperature >38°C (100.4°F), tonsillar exudate, age of individual.
- Patients with recurrent infections (>7 episodes in the preceding year or >5 in the preceding 2 years or >4 in the preceding 3 years): Consider tonsillectomy.
- Patients with obstructive SDB diagnosed by polysomnography: Perform adenoidectomy and tonsillectomy.

ACUTE AND CHRONIC LARYNGITIS

Laryngitis results from laryngeal inflammation due to several factors: excessive coughing, infections, vocal abuse/strain, gastroesophageal reflux, irritants such as smoking. Chronic laryngitis usually results from multiple factors leading over time to persistent inflammation.

History/PE

- **Acute:** Less than 3 weeks of hoarseness.
- **Chronic:** More than 3 weeks of hoarseness.
- History of the chief complaint reveals aforementioned inciting factors.

Diagnosis

- Perform physical examination of the head and neck (lymph nodes can be suggestive of malignancy).
- In select cases, perform nasopharyngoscopy to visualize the vocal cords (lesions on the vocal cord such as polyps or nodules, bilateral motion of the vocal cords, edema).

Treatment

- Supportive management is often needed with vocal hygiene (absolute silence is not required), hydration, cough suppression, and avoidance of precipitating/irritating factors such as smoking.
- Proton pump inhibitors are needed if reflux is suspected or diagnosed.

LARYNGOPHARYNGEAL REFLUX

Reflux of caustic gastric contents causing irritation of laryngeal tissue. Related to resting upper and lower esophageal sphincter tone and also to duration/magnitude of increased intra-abdominal pressure (eg, obesity would cause chronic increased intra-abdominal pressure).

History/PE

- Dysphonia
- Cough
- Globus

- Throat clearing
- Dysphagia

Diagnosis

Largely based on clinical signs/symptoms

Treatment

- Dietary changes (avoidance of caffeine, chocolate, peppermint, alcohol, and acidic foods)
- Behavioral changes (avoidance of smoking, waiting 2 hours after eating for vigorous exercise, avoidance of eating/drinking 3 hours before sleep)
- Acid suppression (proton pump inhibitors [PPIs], H_2 antagonist)

BENIGN AND MALIGNANT LARYNGEAL LESIONS

Vocal Cord Polyp

Most common benign laryngeal lesion. Typically caused by vocal cord overuse (eg, singers, teachers), smoking, and/or gastroesophageal reflux disease (GERD).

- ***Hx/PE:*** Presents with hoarseness and, in severe cases, dyspnea
- ***Dx:*** Laryngoscopy or stroboscopy
- ***Tx:*** Voice therapy, microsurgery

Vocal Cord Nodule

Typically caused by vocal cord overuse (eg, singers, teachers), smoking, and/or GERD. Presents with hoarseness.

- ***Dx:*** Laryngoscopy or stroboscopy
- ***Tx:*** Voice therapy, smoking cessation, PPI if GERD symptoms present, steroid injections, microsurgery

Recurrent Respiratory Papillomatosis

- Recurrent respiratory papillomatosis is a rare disease caused by human papillomavirus (HPV) infection of the upper airway, resulting in warty growths.
- In about 3% to 5% of patients, malignant transformation to squamous cell carcinoma may occur.
- The juvenile form is due to peripartum transmission from an infected mother. Children may need up to 20 repeat procedures during their lifetime, causing significant morbidity; however, remission may occur after several years.
- The adult form is probably transmitted through oral sex.

Risk Factors

- Juvenile form: Triad of being firstborn, vaginal delivery, and mother's age <20 years. Other risks include lower socioeconomic status. The physician should consider sexual abuse in children older than 5 years.
- Adult form: More lifetime sexual partners and increased frequency of oral sex.

History/PE

Hoarseness (most common), voice change, episodic choking, foreign body sensation, cough, dyspnea, inspiratory wheeze, and stridor.

Diagnosis

Laryngoscopy or bronchoscopy.

Treatment

- there is no cure.
- repeated surgical debulking is mainstay of treatment. Cidofovir is injected in resection site in select patients.
- subcutaneous interferon therapy may be useful as second line.
- tracheostomy is used for significant airway obstruction.
- prevention is through quadrivalent HPV vaccination.

HIGH-YIELD FACTS IN

RENAL/GENITOURINARY

Electrolyte Disorders
  - HYPERNATREMIA
  - HYPONATREMIA
  - HYPERKALEMIA
  - HYPOKALEMIA
  - HYPERCALCEMIA
  - HYPOCALCEMIA
  - HYPOMAGNESEMIA

Acid-Base Disorders
  - URINE ANION GAP

Renal Tubular Acidosis

Acute Kidney Injury

Chronic Kidney Disease

Diuretics

Glomerular Disease
  - NEPHRITIC SYNDROME
  - NEPHROTIC SYNDROME

Nephrolithiasis

Polycystic Kidney Disease

Hydronephrosis

Scrotal Pain and Swelling

Urinary Incontinence

Interstitial Cystitis (Painful Bladder Syndrome)

Erectile Dysfunction

Benign Prostatic Hyperplasia

Urologic Cancer
  - PROSTATE CANCER
  - BLADDER CANCER
  - RENAL CELL CARCINOMA
  - TESTICULAR CANCER

Genitourinary Infections

URINARY TRACT INFECTIONS
UNCOMPLICATED UTI/LOWER UTI/ACUTE SIMPLE CYSTITIS
PYELONEPHRITIS/UPPER UTI/ONE FORM OF COMPLICATED UTI
PROSTATITIS: ONE FORM OF COMPLICATED UTI

Sexually Transmitted Diseases
CHLAMYDIA
GONORRHEA
SYPHILIS
GENITAL LESIONS

ELECTROLYTE DISORDERS

HYPERNATREMIA

Serum sodium >145 mEq/L. Usually caused by free water loss rather than sodium gain.

KEY FACT

Certain patients (eg, infants, intubated patients, immobilized patients, and those with altered mental status) may not drink enough free water to replace insensible losses. This can cause or worsen hypernatremia.

History/PE

Often presents with thirst caused by hypertonicity. Patients can present with neurologic symptoms including altered mental status, weakness, focal neurologic deficits, and seizures.

Diagnosis

The etiology of hypernatremia can be determined by measuring urine osmolality.

- If urine osmolality is >600 mOsm/kg, hypernatremia most likely stems from extrarenal water loss (insensible losses, nasogastric tube suction, diarrhea) or excess sodium intake. Measuring urine sodium through a fractional excretion of sodium can be helpful in distinguishing extrarenal losses (<1%) from sodium gain (>2%).
- If urine osmolality is <300 mOsm/kg, diabetes insipidus (DI) is the most likely cause of hypernatremia. A desmopressin challenge can differentiate between central and nephrogenic DI.
  - Rise in urine osmolality with desmopressin = Central DI
  - No rise in urine osmolality with desmopressin = Nephrogenic DI
- Intermediate values (300–600 mOsm/kg) are often seen in osmotic diuresis or partial DI.

Treatment

- Determine volume status. If the patient is hypovolemic with unstable vital signs, use isotonic 0.9% NaCl before correcting free water deficits. Use isotonic 0.9% NaCl until the patient is approaching euvolemia.
- Determine free water deficit.
  - $\text{Water deficit} = \text{Total body water} \times ([\text{serum Na}/140] - 1)$.

  - Total body water (TBW) is ~60% of lean body weight (in kg).
- Determine rate of correction. Correction of chronic hypernatremia (duration >48 hours) should be accomplished gradually over 48 to 72 hours (≤0.5 mEq/L/hr) to prevent neurologic damage secondary to cerebral edema. In acute hypernatremia (<48 hours), the entire free water deficit can be corrected within 24 hours.
- Free water deficit can then be corrected with dextrose 5% water (D_5W), 0.45% NaCl, or enteral fluids.

MNEMONIC

Causes of hypernatremia—

The 6 Ds

Diuresis
Dehydration
Diabetes insipidus
Docs (iatrogenic)
Diarrhea
Disease (eg, kidney, sickle cell)

HYPONATREMIA

Serum sodium <135 mEq/L. Hyponatremia is most commonly caused by ↑ ADH, whether physiologic (eg, in decreased effective circulating volume) or pathologic (as in syndrome of inappropriate secretion of antidiuretic hormone [SIADH]). There are some ADH-independent etiologies, such as primary polydipsia, starvation (solute deficiency), and the presence of a nonsodium effective osmole in the extracellular fluid (eg, glucose in hyperglycemia).

History/PE

- May be asymptomatic, but can present with confusion, lethargy, muscle cramps, and nausea.
- Can progress to seizures, coma, or brainstem herniation. Severity of symptoms depends on rate and degree of hyponatremia.

Diagnosis

- Measure serum osmolality (sOsm). Hypotonic hyponatremia (sOsm <280) is the most common type of hyponatremia and is further categorized by volume status. See Figure 2.15-1 for the full diagnostic algorithm.

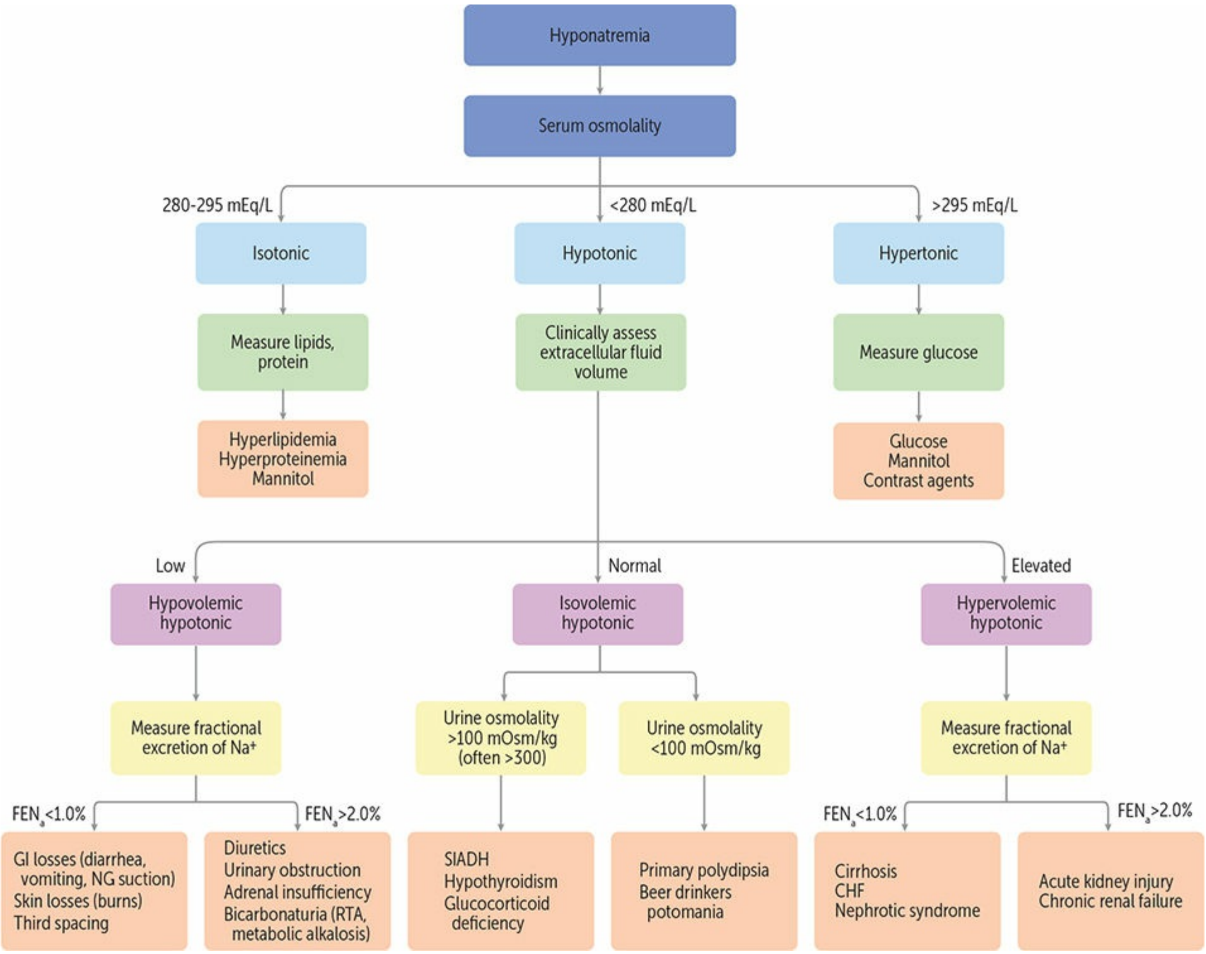

Hyponatremia
Serum osmolality
280-295 mEq/L
<280 mEq/L
>295 mEq/L
Isotonic
Hypotonic
Hypertonic
Measure lipids, protein
Clinically assess extracellular fluid volume
Measure glucose
Hyperlipidemia
Hyperproteinemia
Mannitol
Glucose
Mannitol
Contrast agents
Low
Normal
Elevated
Hypovolemic hypotonic
Isovolemic hypotonic
Hypervolemic hypotonic
Measure fractional excretion of Na+
Urine osmolality >100 mOsm/kg (often >300)
Urine osmolality <100 mOsm/kg
Measure fractional excretion of Na+
FENa <1.0%
FENa >2.0%
FENa <1.0%
FENa >2.0%
GI losses (diarrhea, vomiting, NG suction)
Skin losses (burns)
Third spacing
Diuretics
Urinary obstruction
Adrenal insufficiency
Bicarbonaturia (RTA, metabolic alkalosis)
SIADH
Hypothyroidism
Glucocorticoid deficiency
Primary polydipsia
Beer drinkers
potomania
Cirrhosis
CHF
Nephrotic syndrome
Acute kidney injury
Chronic renal failure

FIGURE 2.15-1. **Diagnostic algorithm for hyponatremia.** Boxes highlighted in yellow represent key lab tests to perform. (Reproduced with permission from USMLE-Rx.com.)

- Hypertonic hyponatremia (sOsm >295) is secondary to increased concentration of effective osmotic solute. This is commonly seen in hyperglycemia. Be sure to "correct" serum sodium for hyperglycemia by adding 1.6 mEq/L to the sodium for every 100 mg/dL elevation in glucose above 200 mg/dL. For example, a patient with a measured serum sodium concentration of 133 mEq/L and a blood glucose concentration of 400 mg/dL actually has a serum sodium concentration closer to 136 mEq/L.
- Isotonic hyponatremia (sOsm 280–295) is most commonly due to a laboratory measurement artifact. Conditions such as hyperlipidemia/hypertriglyceridemia or hyperproteinemia (after intravenous [IV] immunoglobulin infusion or in multiple myeloma) increase the solid phase of plasma, meaning there is less water (where sodium is diluted) in the analyzed sample, which is not corrected by the machine.

Q

A 29-year-old woman with a history of bipolar disorder presents to the emergency department with altered mental status. On examination she seems hypovolemic, with vitals measured at blood pressure (BP) of 92/50 mm Hg and heart rate (HR) of 106 beats per minute (bpm). Her serum sodium level is 154 mEq/L. What is the next best step in management?

Treatment

- Treat the underlying disorder. Treat hyponatremia from hypervolemic and euvolemic etiologies with water restriction ± diuretics. If hypovolemic, replete volume with NaCl. If severe hyponatremia (Na <120 mEq/L), consider 3% hypertonic saline, particularly if symptomatic (eg, seizures).
- Correct chronic hyponatremia (>72 hours' duration) slowly (<10 mEq/L/day) to prevent osmotic demyelination syndrome (symptoms include paraparesis/quadriparesis, dysarthria, and coma). See Figure 2.15-2.

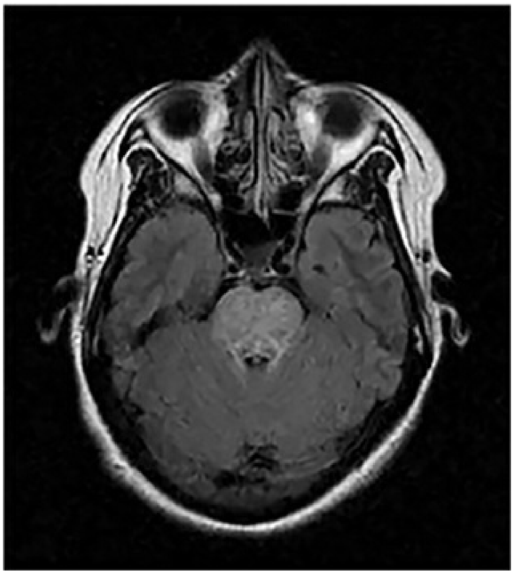


FIGURE 2.15-2. Osmotic demyelination syndrome on MRI. (Adapted with permission from Chang KY, Lee IH, Kim GJ, et al. Plasma exchange successfully treats central pontine myelinolysis after acute hypernatremia from intravenous sodium bicarbonate therapy. *BMC Nephrol.* 2014;15:56. doi:10.1186/1471-2369-15-56.)

KEY FACT

Consider using hypertonic saline only if a patient has seizures or acute neurologic decline caused by hyponatremia and when serum Na+ is <120 mEq/L.

KEY FACT

Correcting hyponatremia too rapidly can lead to osmotic demyelination syndrome.

HYPERKALEMIA

Serum potassium (K^+) >5 mEq/L. Etiologies include:

- **Spurious:** Hemolysis of blood samples, fist clenching during blood draws, delays in sample analysis, extreme leukocytosis or thrombocytosis
- ↓ **excretion:** Renal insufficiency, drugs (eg, spironolactone, triamterene, amiloride, angiotensin-converting enzyme [ACE] inhibitors, trimethoprim, nonsteroidal anti-inflammatory drugs [NSAIDs], nonselective β-blockers), hypoaldosteronism, type IV renal tubular acidosis (RTA), calcineurin inhibitors
- **Cellular shifts:** Cell lysis, tissue injury (rhabdomyolysis), tumor lysis syndrome, insulin

deficiency, acidosis, drugs (eg, succinylcholine, digitalis, arginine, nonselective β-blockers), hyperosmolality, exercise

- ↑ **intake:** Food (most fruits, potatoes), iatrogenic, absorption of blood (from hematomas, gastrointestinal [GI] bleeding)

History/PE

May be asymptomatic or may present with nausea, vomiting, intestinal colic, areflexia, weakness, flaccid paralysis, arrhythmias, and/or paresthesia.

Diagnosis

- Confirmation of hyperkalemia with a repeat blood draw for suspected spurious results. In the setting of extreme leukocytosis or thrombocytosis, the physician should check plasma K^+ (as opposed to serum K^+, since potassium can be released from cells in serum and falsely elevate the result).
- **Other workup:** ECG to evaluate for cardiac complications. ECG findings include tall, peaked T waves; a wide QRS; PR prolongation; and loss of P waves (see Fig. 2.15-3). Can progress to sine waves, ventricular dysrhythmias, and cardiac arrest.

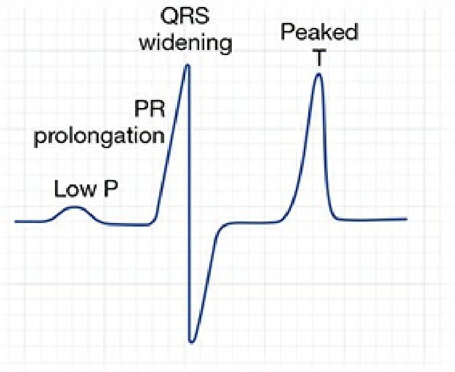


FIGURE 2.15-3. **Hyperkalemia on ECG.** Electrocardiographic manifestations include peaked T waves, PR prolongation, and a widened QRS complex. (Reproduced with permission from USMLE-Rx.com.)

Treatment

- **Best initial treatment:** It is critical to administer calcium gluconate for cardiac cell membrane stabilization if K^+ >6.5 mEq/L or if ECG changes are present.
- Give insulin with glucose (to avoid hypoglycemia), β-agonists (eg, continuous inhaled albuterol), and/or alkali (eg, bicarbonate) to temporarily shift K^+ into cells. This is the most rapid way to shift K^+ into cells.
- Remove K^+ from the body. If the patient has residual renal function (ie, they are not anuric/oliguric), consider IV saline (in the setting of hypovolemia) or loop diuretics (in normovolemia/hypervolemia) to enhance urinary excretion of potassium. Kayexalate (sodium polystyrene sulfonate) is a medication that exchanges sodium for potassium in the bowel and can be used to excrete potassium in the setting of a lack of residual renal function. Contraindications to this include ileus, bowel obstruction, ischemic gut, or pancreatic transplants (can cause bowel necrosis).

A

This patient probably has nephrogenic diabetes insipidus from presumed lithium use. She is hypovolemic with unstable vital signs; therefore, the next best step in management calls for initial treatment with normal saline (NS), followed by a switch to D_5W once her volume status improves.

- Eliminate K^+ from the diet, medications (eg, penicillin has K^+), and IV fluids.
- Dialysis is needed for patients with renal failure and hyperkalemia refractory to the aforementioned medical management.

HYPOKALEMIA

Serum K^+ <3.6 mEq/L. Etiologies include:

- **Transcellular shifts:** Insulin, β_2-agonists, and alkalosis all cause K^+ to shift intracellularly (see Fig. 2.15-4).

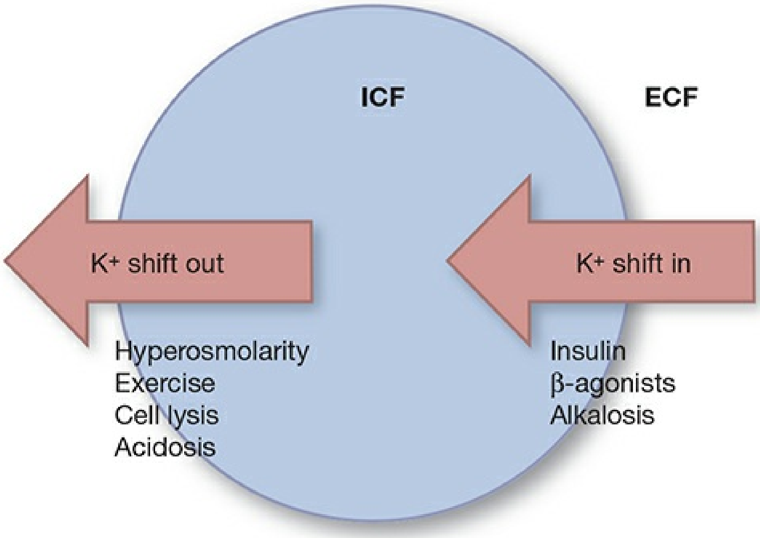


FIGURE 2.15-4. **Causes of transcellular K^+ shifts.** *ECF*, Extracellular fluid; *ICF*, intracellular fluid. (Reproduced with permission from USMLE-Rx.com.)

- **GI losses:** Diarrhea, chronic laxative abuse, vomiting, nasogastric tube suction.
- **Renal losses:** Diuretics (eg, loop or thiazide), primary mineralocorticoid excess or secondary hyperaldosteronism, ↓ circulating volume (stimulates renin-angiotensin-aldosterone system [RAAS]⁻ and mineralocorticoid-associated K^+ secretion), Bartter and Gitelman syndromes, drugs (eg, gentamicin, amphotericin), diabetic ketoacidosis, hypomagnesemia, type I and type II RTA.

KEY FACT

If a patient is on digitalis, K^+ levels must be carefully monitored. Hypokalemia sensitizes the heart to digitalis toxicity, because K^+ and digitalis compete for the same sites on the Na^+/K^+ pump.

History/PE

Hypokalemia is usually asymptomatic, but it can present with fatigue, muscle weakness or cramps, ileus, hyporeflexia, paresthesias, rhabdomyolysis, and ascending paralysis.

Diagnosis

Other workup: ECG may show T-wave flattening, U waves (an additional wave after the T wave), and ST-segment depression, leading to atrioventricular (AV) block and subsequent cardiac arrest. See Figure 2.15-5.

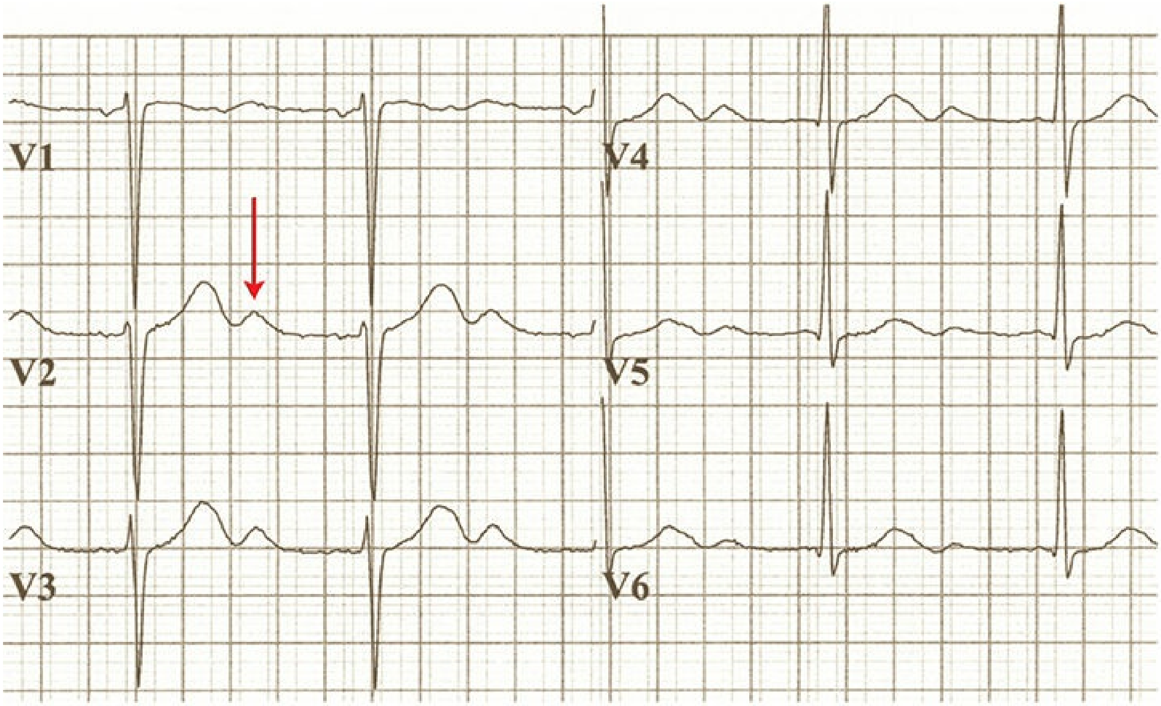


FIGURE 2.15-5. Hypokalemia on ECG. Prominent U wave indicated by *arrow*. (Reproduced with permission from Van Beers EJ, Stam J, van den Bergh WM. Licorice consumption as a cause of posterior reversible encephalopathy syndrome: a case report. *Crit Care.* 2011;15[1]:R64.)

KEY FACT

Hypokalemia is usually caused by renal ± GI losses.

Treatment

- Treat the underlying disorder.
- Oral and/or IV K^+ repletion. Oral is the preferred route for safety purposes. If IV is necessary, a continuous rate of K^+ as an additive is preferred over an IV K^+ bolus. IV boluses should be reserved for symptomatic hypokalemia or ECG changes. Treatment should not exceed 20 mEq/L/hr.
- Replacement of magnesium. This deficiency makes K^+ repletion more difficult.

KEY FACT

If hypokalemia is not responding to K^+ repletion, check magnesium levels.

MNEMONIC

Treatment of hyperkalemia—

C BIG K

Calcium chloride or gluconate (intravenous)
Bicarbonate, β_2-agonists
Insulin + **G**lucose
Kayexalate (sodium polystyrene sulfonate)

HYPERCALCEMIA

Serum calcium >10.2 mg/dL. The most common causes are the following:

- Hyperparathyroidism
- Malignancy (eg, breast cancer, squamous cell carcinoma, multiple myeloma)
- Other causes in the mnemonic CHIMPANZEES. See Mnemonic box.

MNEMONIC

Causes of hypercalcemia—

CHIMPANZEES

Calcium supplementation
Hyperparathyroidism/**H**yperthyroidism
Iatrogenic (eg, thiazides, parenteral nutrition)/**I**mmobility (especially in the intensive care unit [ICU] setting)
Milk-alkali syndrome (excessive intake of calcium and absorbable alkali)
Paget disease
Adrenal insufficiency/**A**cromegaly
Neoplasm
Zollinger-Ellison syndrome (eg, multiple endocrine neoplasia [MEN] type 1)
Excess vitamin A
Excess vitamin D
Sarcoidosis and other granulomatous diseases

History/PE

Usually asymptomatic but can present with *bones* (osteopenia, fractures), *stones* (kidney stones), *abdominal groans* (anorexia, constipation), and *psychiatric overtones* (weakness, fatigue, irritability, altered mental status).

Diagnosis

- **Best initial test:** Check of total/ionized calcium and albumin. Reasoning: A large portion of serum calcium is albumin bound, and changes in albumin concentration can lead to alterations in serum calcium concentration that do not necessarily affect ionized calcium (the physiologically active form.) In general, when correcting for serum albumin concentration, the physician can assume that serum calcium falls by 0.8 mg/dL for every 1 g/dL decrease in serum albumin below 4 g/dL.

- **Also consider:** Phosphate, magnesium, parathyroid hormone (PTH), creatinine, alkaline phosphatase levels. The following tests apply: parathyroid hormone–related peptide (PTHrP) if malignancy is suspected; serum protein electrophoresis for multiple myeloma; vitamin D (total 25 vitamin D and 1,25 vitamin D levels) if granulomatous disease (eg, sarcoidosis), iatrogenic vitamin D intake, or tuberculosis (TB) is suspected.
- **Other workup:** ECG may show shortened QT interval.
- See Figure 2.15-6 for diagnostic testing algorithm.

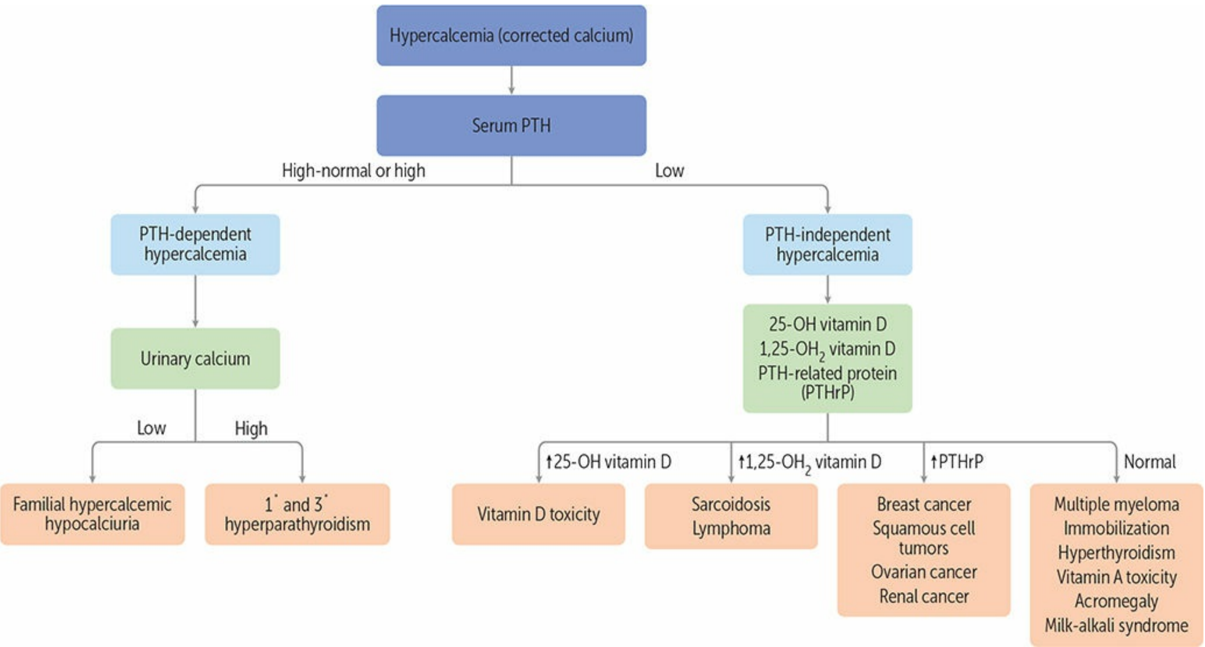

Hypercalcemia (corrected calcium)
Serum PTH
High-normal or high
Low
PTH-dependent hypercalcemia
PTH-independent hypercalcemia
Urinary calcium
Low
High
Familial hypercalcemic hypocalciuria
1° and 3° hyperparathyroidism
25-OH vitamin D
1,25-OH$_2$ vitamin D
PTH-related protein (PTHrP)
↑25-OH vitamin D
↑1,25-OH$_2$ vitamin D
↑PTHrP
Normal
Vitamin D toxicity
Sarcoidosis
Lymphoma
Breast cancer
Squamous cell tumors
Ovarian cancer
Renal cancer
Multiple myeloma
Immobilization
Hyperthyroidism
Vitamin A toxicity
Acromegaly
Milk-alkali syndrome

FIGURE 2.15-6. **Diagnostic testing algorithm for evaluation of hypercalcemia.** (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

Serum calcium levels may be incidentally low in hypoalbuminemia; check ionized calcium. Corrected Ca^{2}+ = Total serum Ca^{2}+ + 0.8 (4 − serum albumin).

Treatment

- The physician should treat the underlying disorder.
- Mild hypercalcemia (albumin-corrected calcium <12 mg/dL) does not require urgent treatment. Patients should be encouraged to maintain adequate hydration (to avoid nephrolithiasis) and to avoid factors that worsen hypercalcemia (thiazides, high calcium intake, inactivity).
- If serum calcium >14 mg/dL, a patient requires urgent treatment with isotonic IV fluids (± furosemide) and calcitonin; bisphosphonates (eg, zoledronic acid, pamidronate) should be considered as well. High sodium intake (in isotonic fluids) facilitates renal calcium excretion and prevents renal complications (stones).
- Asymptomatic patients with serum calcium between 12 and 14 mg/dL do not require emergent treatment—they may follow the same precautions noted earlier for mild hypercalcemia, as well as some therapies (eg, isotonic fluids) to facilitate excretion of

calcium before symptoms develop.

KEY FACT

Loop diuretics (furosemide) **L**ose calcium. **T**hiazide diuretics ↑ **T**ubular reabsorption of calcium.

HYPOCALCEMIA

Serum calcium <8.5 mg/dL. Etiologies include the following:

- **Parathyroid-related:** Hypoparathyroidism (postsurgical, idiopathic), chronic kidney disease (causing secondary hyperparathyroidism), and pseudohypoparathyroidism (PTH resistance). In infants, consider abnormal parathyroid development in DiGeorge syndrome.
- Malnutrition, vitamin D deficiency.
- **Other:** Hypomagnesemia, acute pancreatitis, and chelation from citrate found in blood products.

History/PE

- Hypocalcemia presents with abdominal muscle cramps, dyspnea, tetany, perioral and acral paresthesias, and convulsions.
- Facial spasms elicited from tapping of the facial nerve (Chvostek sign) and carpal spasms after arterial occlusion by a blood pressure (BP) cuff (Trousseau sign) are classic findings most commonly seen in severe hypocalcemia.

KEY FACT

A classic case of hypocalcemia is a patient who develops cramps and tetany following thyroidectomy because of parathyroidectomy as a complication.

KEY FACT

Hypomagnesemia is very commonly seen in the setting of chronic excessive alcohol consumption.

KEY FACT

Acetylsalicylic acid ([ASA] salicylate) overdose can cause both metabolic acidosis and respiratory alkalosis.

KEY FACT

Ethylene glycol presentation = Urine calcium oxalate (envelope-shaped) crystals
Methanol presentation = Vision loss, optic disc hyperemia

Both present with ↑ osmolal gap (measured osmolality − calculated osmolality >10 mOsmol/L)

Diagnosis

- **Most accurate test:** Ionized Ca^{2+} and PTH. See the Endocrinology chapter for interpretation of PTH levels.
- **Other labs:** Mg^{2+} (low levels can induce PTH resistance); albumin; 25-OH vitamin D; 1,25-OH vitamin D levels; and electrolytes. Blood urea nitrogen (BUN), creatinine, and alkaline phosphatase values may also be helpful to assess, depending on the clinical situation.
- **Other workup:** ECG may show prolonged QT interval.

Treatment

- Treat the underlying disorder.
- In most cases, the physician will need to administer oral calcium supplements; severe symptoms or signs call for oral and IV calcium.
- Ensure magnesium repletion.

HYPOMAGNESEMIA

Serum magnesium <1.5 mEq/L. Etiologies are as follows:

- ↓ **intake:** Malnutrition, malabsorption, short bowel syndrome, total parenteral nutrition (TPN), proton pump inhibitors (PPIs)
- ↑ **loss:** Diuretics, diarrhea, vomiting, hypercalcemia, excessive alcohol consumption
- **Miscellaneous:** Diabetic ketoacidosis, pancreatitis, extracellular fluid volume expansion

History/PE

In severe cases, symptoms may include hyperactive reflexes, tetany, paresthesias, irritability, confusion, lethargy, seizures, and arrhythmias.

Diagnosis

- Lab results may show concurrent hypocalcemia and hypokalemia.
- ECG may reveal prolonged PR and QT intervals.

Treatment

- Generally, most causes respond to IV and/or oral supplements, depending on severity.
- Hypokalemia and hypocalcemia will not correct without magnesium correction.

MNEMONIC

Specific treatments for anion gap causes of metabolic acidosis—
MUDPILES

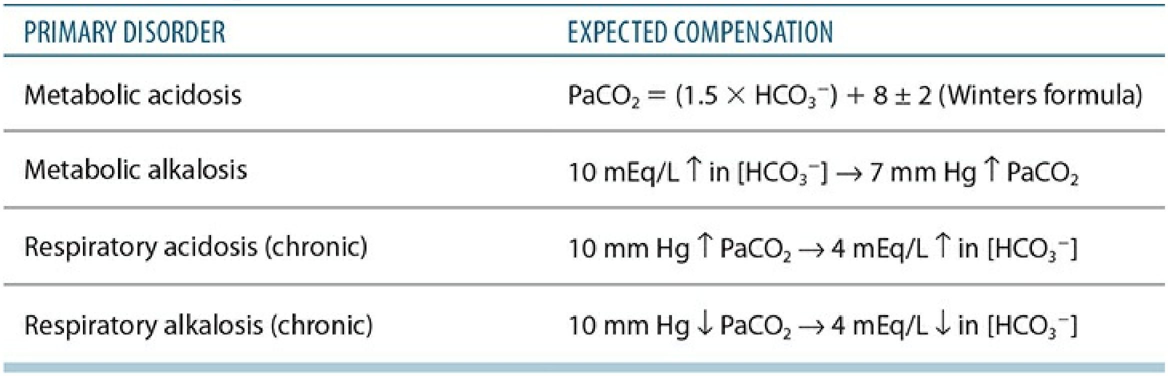
Methanol: Fomepizole
Uremia: Dialysis
Diabetic ketoacidosis: Insulin, isotonic IV fluids, K^+ repletion

Paraldehyde, **P**henformin
Iron, **I**NH: GI lavage, charcoal (isoniazid [INH])
Lactic acidosis: Correct underlying cause; if from ischemia, then responds to repletion of circulating volume
Ethylene glycol: Fomepizole
Salicylates: Isotonic IV fluids with added sodium bicarbonate to alkalinize urine

ACID-BASE DISORDERS

Table 2.15-1 lists expected compensation for acid-base disorders. See Figure 2.15-7 for a diagnostic algorithm of acid-base disorders.

TABLE 2.15-1. Compensation for Acid-Base Disorders



PRIMARY DISORDER	EXPECTED COMPENSATION
Metabolic acidosis	$PaCO_2 = (1.5 \times HCO_3^-) + 8 \pm 2$ (Winters formula)
Metabolic alkalosis	10 mEq/L ↑ in $[HCO_3^-]$ → 7 mm Hg ↑ $PaCO_2$
Respiratory acidosis (chronic)	10 mm Hg ↑ $PaCO_2$ → 4 mEq/L ↑ in $[HCO_3^-]$
Respiratory alkalosis (chronic)	10 mm Hg ↓ $PaCO_2$ → 4 mEq/L ↓ in $[HCO_3^-]$

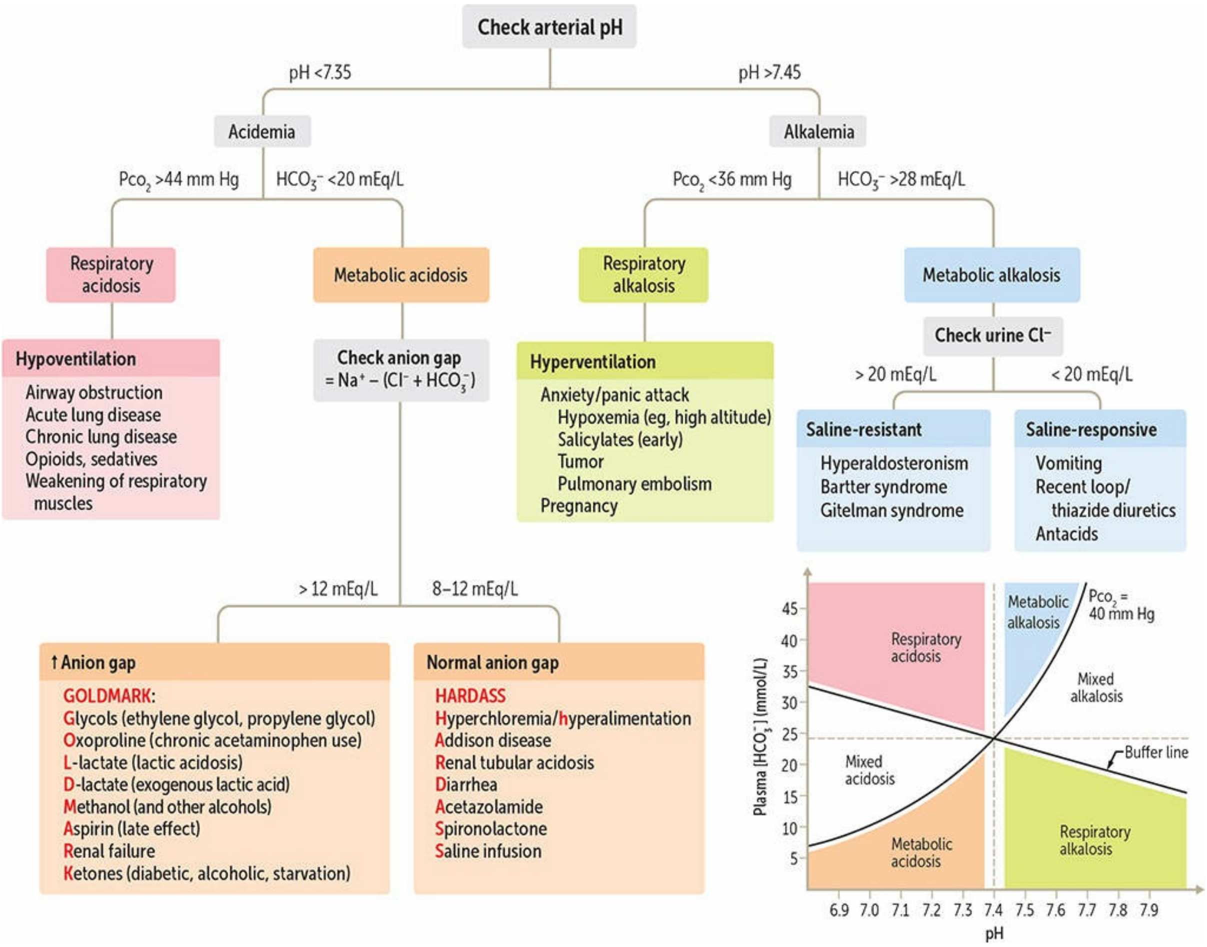

Check arterial pH
pH <7.35
pH >7.45
Acidemia
Alkalemia
Pco2 >44 mm Hg
HCO3− <20 mEq/L
Pco2 <36 mm Hg
HCO3− >28 mEq/L
Respiratory acidosis
Metabolic acidosis
Respiratory alkalosis
Metabolic alkalosis
Hypoventilation
Airway obstruction
Acute lung disease
Chronic lung disease
Opioids, sedatives
Weakening of respiratory muscles
Check anion gap = Na+ − (Cl− + HCO3−)
Hyperventilation
Anxiety/panic attack
Hypoxemia (eg, high altitude)
Salicylates (early)
Tumor
Pulmonary embolism
Pregnancy
Check urine Cl−
> 20 mEq/L
< 20 mEq/L
Saline-resistant
Hyperaldosteronism
Bartter syndrome
Gitelman syndrome
Saline-responsive
Vomiting
Recent loop/thiazide diuretics
Antacids
> 12 mEq/L
8–12 mEq/L
↑Anion gap
GOLDMARK:
Glycols (ethylene glycol, propylene glycol)
Oxoproline (chronic acetaminophen use)
L-lactate (lactic acidosis)
D-lactate (exogenous lactic acid)
Methanol (and other alcohols)
Aspirin (late effect)
Renal failure
Ketones (diabetic, alcoholic, starvation)
Normal anion gap
HARDASS
Hyperchloremia/hyperalimentation
Addison disease
Renal tubular acidosis
Diarrhea
Acetazolamide
Spironolactone
Saline infusion
Plasma [HCO3−] (mmol/L)
45
40
35
30
25
20
15
10
5
Respiratory acidosis
Metabolic alkalosis
Pco2 = 40 mm Hg
Mixed alkalosis
Buffer line
Mixed acidosis
Metabolic acidosis
Respiratory alkalosis
6.9 7.0 7.1 7.2 7.3 7.4 7.5 7.6 7.7 7.8 7.9
pH

FIGURE 2.15-7. **Diagnostic algorithm for acid-base disorders.** (Adapted with permission from USMLE-Rx.com.)

URINE ANION GAP

- Calculated for normal anion gap acidosis to distinguish renal vs GI bicarbonate loss.
- Urine anion gap (UAG) = [Urine Na^+] + [Urine K^+] − [Urine Cl^-].
- Urine NH_4^+ (which represents renal acid excretion but is difficult to measure) is excreted along with Cl^- in the urine. A negative UAG indicated increased urine Cl^-, which suggests that acid (NH_4^+) is being excreted by the kidneys. This can be seen in cases of GI HCO_3^- loss or proximal/type 2 RTA.

Q 1

A 26-year-old woman with a history of depression presents to the emergency department with altered mental status, tinnitus, nausea, and vomiting. An arterial blood gas (ABG) assessment shows a pH of 7.4, $Paco_2$ of 22, and a HCO_3^- of 13. What is the most likely diagnosis, and what is her acid-base disorder?

Q 2

A 17-year-old boy with a history of asthma presents to the emergency department with severe shortness of breath. His arterial pH has gone from 7.49 to 7.38 and his Pa_{CO_2} from 30 to 50 mm Hg since the time of admission. What is the next best step in management?

- A ⊕ UAG suggests impaired NH_4^+ excretion, which is seen in cases of distal/type 1 RTA.
- GI bicarbonate loss (eg, diarrhea) → ⊖ UAG

RENAL TUBULAR ACIDOSIS

A net ↓ in either tubular H^+ secretion or HCO_3^- reabsorption that leads to a non–anion gap metabolic acidosis. There are three main types of RTA; type IV (aldosterone deficient/resistant) is the most common form (see Table 2.15-2).

TABLE 2.15-2. Types of Renal Tubular Acidosisw

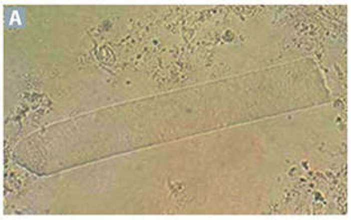
VARIABLE	TYPE I (DISTAL)	TYPE II (PROXIMAL)	TYPE IV (IMPAIRED MINERALOCORTICOID EFFECT)
Defect	H^+ secretion	HCO_3^- reabsorption	Aldosterone deficiency or resistance
Serum K^+	Low	Low	High
Urinary pH	>5.5	≥5.5 at onset, but can be <5.5 once serum is in its acidotic state	Variable (not typically used to differentiate)
Etiologies (most common)	Autoimmune disorders, hypercalciuria, amphotericin B, ifosfamide, genetic disorders	Multiple myeloma, amyloidosis, all other causes of Fanconi syndrome (genetic and acquired), aminoglycosides, ifosfamide, cisplatin, acetazolamide	↓ aldosterone production (eg, diabetic hyporeninism, ACE inhibitors, ARBs, NSAIDs, heparin, cyclosporine, adrenal insufficiency) or aldosterone resistance (eg, K^+-sparing diuretics, nephropathy due to obstruction, TMP-SMX)
Treatment	K^+ bicarbonate supplementation	Treatment of underlying cause, often needs sodium and K^+ bicarbonate supplementation	Depending on etiology, may need mineralocorticoid replacement, sodium bicarbonate supplementation, or K^+ wasting diuretics
Associated conditions	Nephrolithiasis	Rickets, osteomalacia	

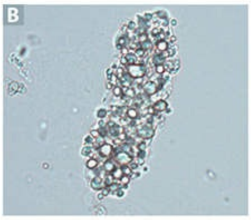
ACUTE KIDNEY INJURY

Formerly known as acute renal failure, acute kidney injury (AKI) is defined as ↓ renal function, compared with a previous baseline within a period of <3 months, leading to the retention of creatinine. ↓ urine output (oliguria, defined as <0.5 mL/kg/hr) is not required for AKI, but if present can be part of the diagnostic criteria. Complications include metabolic acidosis, electrolyte abnormalities, volume overload, and uremia. Many cases of AKI will recover with treatment and/or supportive care, but each episode of AKI can lead to chronic effects and scarring and progressively develop into chronic kidney disease (especially with very severe or recurrent AKI). See Table 2.15-3 for the workup of AKI.

TABLE 2.15-3. Acute Kidney Injury

	PRERENAL	INTRINSIC	POSTRENAL
Pathophysiology	↓ renal perfusion	Injury within the nephron	Urinary outflow obstruction
Common etiologies	Hypovolemia, decreased intravascular volume/fluid displacement (eg, cirrhosis, nephrotic syndrome, increased vascular permeability as in pancreatitis, shock/sepsis), renal artery stenosis, hepatorenal syndrome, drugs (NSAIDs, ACE inhibitors), congestive heart failure (especially with diuretic treatment)	Acute tubular necrosis (ATN) from ischemia or nephrotoxins, glomerulonephritis, embolic disease, rhabdomyolysis Interstitial nephritis (drugs: penicillins, cephalosporins, NSAIDs, sulfa drugs, PPIs, allopurinol)	Prostatic disease, pelvic tumors, intratubular obstruction from crystalluria (acyclovir), bilateral stones, congenital obstructions
History/PE	Symptoms of hypovolemia (tachycardia, hypotension) or other underlying disease process (liver failure, nephrotic syndrome)	History of drug exposure (aminoglycosides, NSAIDs, penicillins, IV contrast media), red- or dark-colored urine	Suprapubic and/or flank pain, distended bladder; bladder scan showing postvoid residual >50 mL
LAB VALUES			
BUN/creatinine ratio	>20:1	<15:1	Varies
Fractional excretion of sodium (Fe_{Na})	<1%	>2%	Varies
Urine sodium	<20 mEq/L	>40 mEq/L	Varies
Urine osmolality	>500 mOsm/kg	<350 mOsm/kg (isosthenuria; damaged tubules cannot reabsorb water or concentrate urine)	Varies
LAB VALUES (continued)			
Urine sediment	Hyaline casts as shown in Image A (normal finding, but in volume depletion)	RBC casts/dysmorphic RBCs as shown in Image B (glomerulonephritis), WBCs/eosinophils, WBC casts (AIN), "muddy-brown or granular casts" as shown in Image C (ATN), WBC casts (pyelonephritis), fatty casts (nephrotic syndrome)	
Treatment	For all etiologies, avoid nephrotic drugs (metformin, NSAIDs) For intrinsic and postrenal etiologies, dialize if meet **AEIOU** criteria and refractory to medical management (see mnemonic)		
	Provide fluids to replete circulating volume if hypovolemic; IV fluids will not help hepatorenal syndrome, nephrotic syndrome, CHF, or other causes of increased total body volume	Prevent contrast nephropathy with IV fluids or nonionic contrast agents; discontinue offending medications; specific therapies as applicable (eg, corticosteroids) for glomerulonephritis	Provide urgent bladder scan and catheterization or relief of obstruction, as applicable





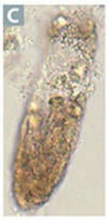


Image A reproduced with permission from USMLE-Rx.com. Images B and C reproduced with permission from USMLE-Rx.com, courtesy of Dr. Adam Weinstein.

KEY FACT

A history of AKI and nephrotoxin exposure should make the physician suspect a diagnosis of acute tubular necrosis (ATN).

MNEMONIC

Indications for urgent dialysis if refractory to medical management—

AEIOU

Acidosis
Electrolyte abnormalities (hyperkalemia)
Ingestions (salicylates, theophylline, methanol, barbiturates, lithium, ethylene glycol)
Overload (fluid)
Uremic symptoms (pericarditis, encephalopathy, bleeding, nausea, pruritus, myoclonus)

CHRONIC KIDNEY DISEASE

Defined as the presence of kidney damage or decreased kidney function (glomerular filtration rate [GFR] <60 mL/min in adults, <90 mL/min in children; persistent proteinuria, or structural damage) for 3 or more months, regardless of the cause. In adults, it is most commonly caused by poorly controlled or long-standing diabetes mellitus (DM) and hypertension. Other causes (in all ages) include:

- Analgesic use (chronic NSAIDs) and chronic use of other nephrotoxic medications
- Renovascular disease, particularly in patients with peripheral arterial disease
- History of prolonged, severe, and/or recurrent AKI
- Severe or recurrent urinary tract infections
- Urinary tract obstruction
- Inherited kidney diseases (such as polycystic kidney disease)
- Glomerular disease
- Congenital abnormalities in kidneys or urinary tract (most common cause in children)

A subset of patients with chronic kidney disease (CKD) will go on to develop CKD stage 5 (GFR <15 mL/min/1.73m^2), which is designated as end-stage renal disease (ESRD) when requiring renal replacement therapy (dialysis).

1 A

The most likely diagnosis is an aspirin overdose. Though her pH is normal, she has a mixed metabolic acidosis and respiratory alkalosis. Her bicarbonate is low, indicating a metabolic acidosis. Winters formula predicts that the patient's Pa_{CO_2} under normal compensation should be 29 [Pa_{CO_2} = 1.5 (HCO_3^-) + 8]. Her Pa_{CO_2} is lower than this at 22, which indicates a concurrent respiratory alkalosis.

2 A

The patient's symptoms and lab results indicate respiratory muscle fatigue. The next best step in management may be urgent intubation.

History/PE

CKD is generally asymptomatic until GFR is <30 mL/min/1.73m^2, but patients can gradually experience the signs and symptoms of disorders such as:

- Hyperkalemia
- Metabolic acidosis
- Secondary hyperparathyroidism (impaired vitamin D activation, decreased phosphate excretion, hypocalcemia, renal osteodystrophy)
- Anemia of CKD
- Uremia (seen most commonly in very advanced CKD—symptoms and complications include anorexia, nausea/vomiting, uremic pericarditis, uremic frost, delirium, impaired platelet aggregation, seizures and coma)

Depending on the etiology, patients can exhibit a varying degree of edema and hypertension because of their reduced ability to excrete salt and water (also seen frequently in those with nephrotic-range proteinuria.)

Diagnosis

A diagnosis of CKD requires persistently impaired renal function or proteinuria, confirmed by repeating laboratory assessment 3 months after initially detected.

Kidney biopsy may need to be considered to determine the etiology of CKD when there is suspicion of glomerulonephritis or unexplained tubulointerstitial disease.

Management

- Ensure tight BP control—target <130/80 mm Hg in adults. ACE inhibitors and angiotensin receptor blockers (ARBs) decrease glomerular filtration pressures and can decrease the rate of progression of proteinuria and CKD (and thus should be the first choice for antihypertensive agents in this population).

KEY FACT

Cardiovascular disease is the most common cause of death in dialysis and renal transplant patients (>50%). Infectious complications are the second most common cause (and most common cause of death in pediatric dialysis and transplant patients).

- Reduce cardiovascular risk by starting statin therapy for patients with CKD over the age of 50 years or for those 18 to 49 years of age with CKD plus a history of coronary artery disease (CAD), DM, or prior stroke.
- Manage anemia—recommend erythropoiesis-stimulating agents (ESAs) for patients with anemia in CKD with a hemoglobin concentration <10 g/dL despite adequate iron stores.
- Monitor serum phosphorus, calcium, and PTH to assess risk for mineral and bone disorders. Manage persistent hyperphosphatemia with oral phosphate binders (calcium acetate, calcium carbonate, sevelamer, lanthanum). Consider calcitriol (1,25-OH vitamin D) for patients with persistent secondary hyperparathyroidism to reduce the risk of osteodystrophy.
- Manage persistent metabolic acidosis (serum bicarbonate <22 mEq/L) with alkali salt

therapy (most commonly oral sodium bicarbonate supplementation).

- Ensure medications are dose adjusted, taking into account the patient’s GFR.
- Patients with a GFR <30 mL/min/1.73m^2 should start education regarding renal replacement therapy (dialysis, transplant). Patients anticipating initiation of hemodialysis should be referred to a vascular surgeon for creation of a fistula.

Q 1

A 68-year-old woman with a history of hepatitis and chronic kidney disease (CKD) presents with right upper quadrant (RUQ) abdominal pain. A CT scan identifies liver cirrhosis. Two days later, her creatinine levels have doubled. What is the likely cause, and what could have prevented this outcome?

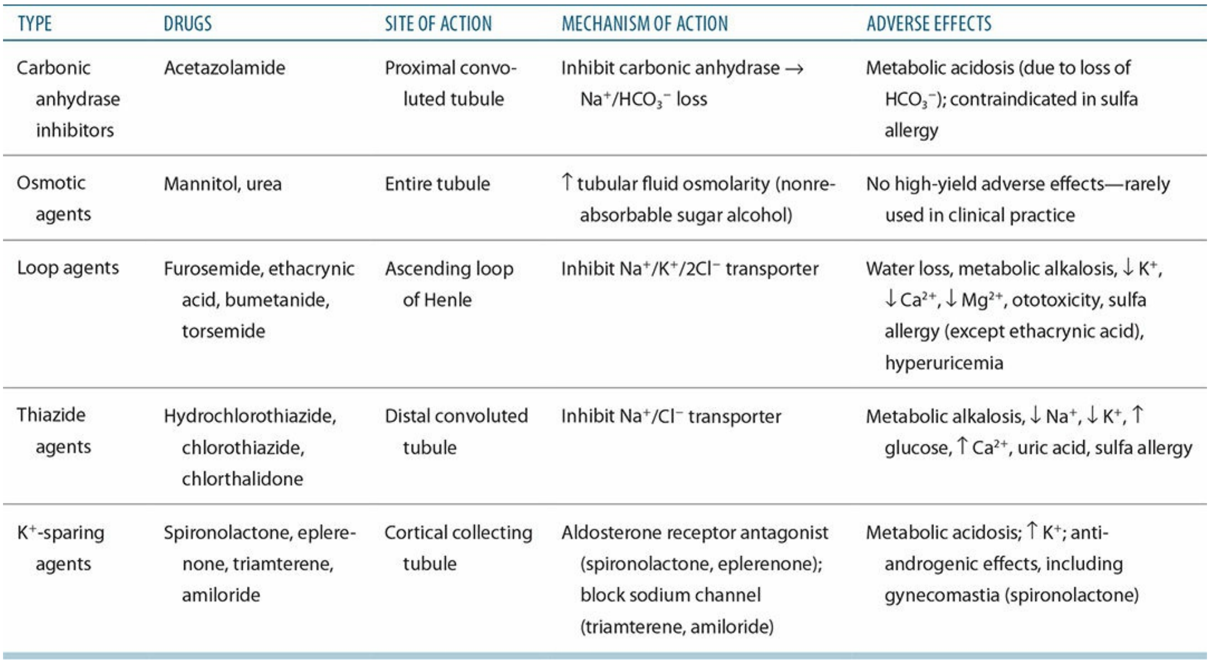
Q 2

A 37-year-old unhoused man was found unconscious on a park bench. Upon waking, he complains of severe muscle soreness and red urine. His urine dipstick is positive for blood, but his urine microscopy has no RBCs. What is the likely cause of this finding, and what is the best next step?

DIURETICS

Table 2.15-4 summarizes the mechanisms of action and adverse effects of commonly used diuretics. Figure 2.15-8 provides a review of nephron physiology with diuretic sites of action.

TABLE 2.15-4. Mechanisms of Action and Adverse Effects of Diuretics



TYPE	DRUGS	SITE OF ACTION	MECHANISM OF ACTION	ADVERSE EFFECTS
Carbonic anhydrase inhibitors	Acetazolamide	Proximal convoluted tubule	Inhibit carbonic anhydrase → Na^+/HCO_3^- loss	Metabolic acidosis (due to loss of HCO_3^-); contraindicated in sulfa allergy
Osmotic agents	Mannitol, urea	Entire tubule	↑ tubular fluid osmolarity (nonreabsorbable sugar alcohol)	No high-yield adverse effects—rarely used in clinical practice
Loop agents	Furosemide, ethacrynic acid, bumetanide, torsemide	Ascending loop of Henle	Inhibit $Na^+/K^+/2Cl^-$ transporter	Water loss, metabolic alkalosis, ↓ K^+, ↓ Ca^{2+}, ↓ Mg^{2+}, ototoxicity, sulfa allergy (except ethacrynic acid), hyperuricemia
Thiazide agents	Hydrochlorothiazide, chlorothiazide, chlorthalidone	Distal convoluted tubule	Inhibit Na^+/Cl^- transporter	Metabolic alkalosis, ↓ Na^+, ↓ K^+, ↑ glucose, ↑ Ca^{2+}, uric acid, sulfa allergy
K^+-sparing agents	Spironolactone, eplerenone, triamterene, amiloride	Cortical collecting tubule	Aldosterone receptor antagonist (spironolactone, eplerenone); block sodium channel (triamterene, amiloride)	Metabolic acidosis; ↑ K^+; antiandrogenic effects, including gynecomastia (spironolactone)

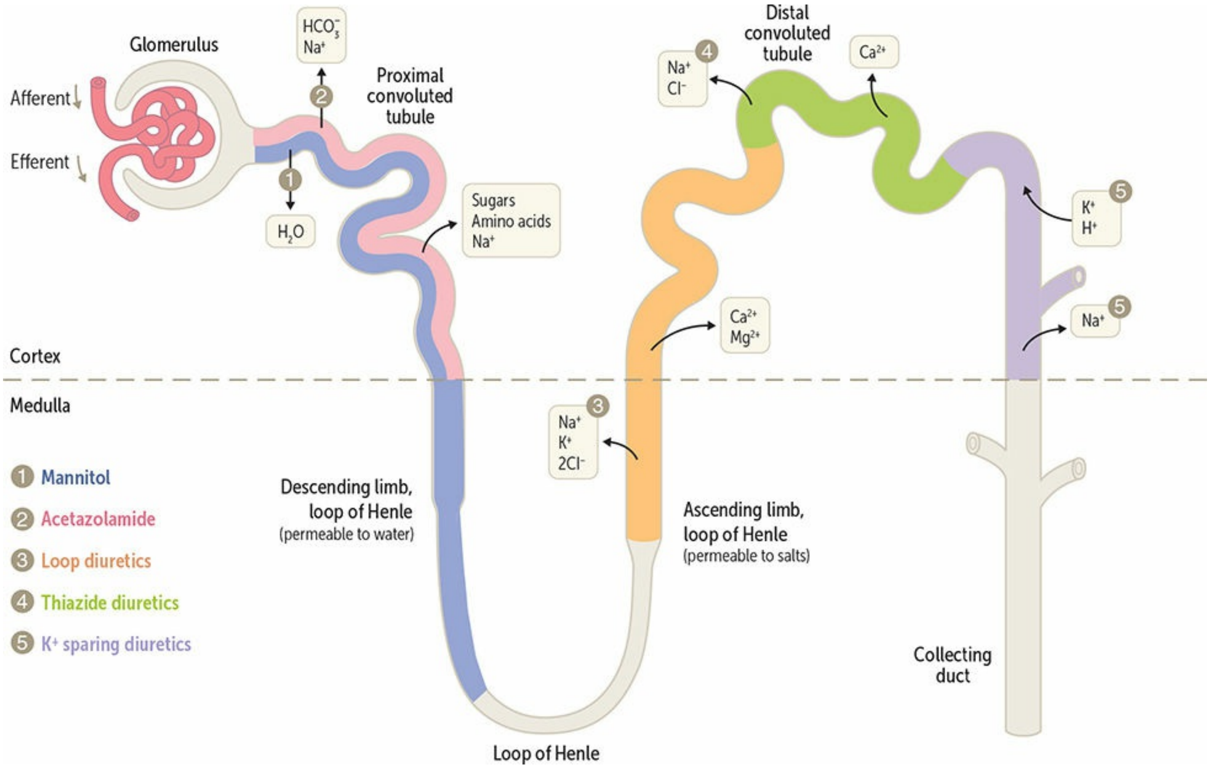

Glomerulus
Afferent
Efferent
HCO_3^-
Na^+
2
Proximal convoluted tubule
1
H_2O
Sugars
Amino acids
Na^+
Distal convoluted tubule
4
Na^+
Cl^-
Ca^{2+}
5
K^+
H^+
5
Na^+
Ca^{2+}
Mg^{2+}
Cortex
Medulla
3
Na^+
K^+
$2Cl^-$
1 Mannitol
2 Acetazolamide
3 Loop diuretics
4 Thiazide diuretics
5 K^+ sparing diuretics
Descending limb, loop of Henle
(permeable to water)
Ascending limb, loop of Henle
(permeable to salts)
Collecting duct
Loop of Henle

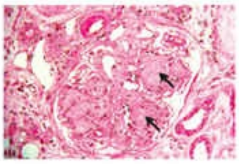
FIGURE 2.15-8. **Diuretics: Site of action.** (Adapted with permission from USMLE-Rx.com.)

GLOMERULAR DISEASE

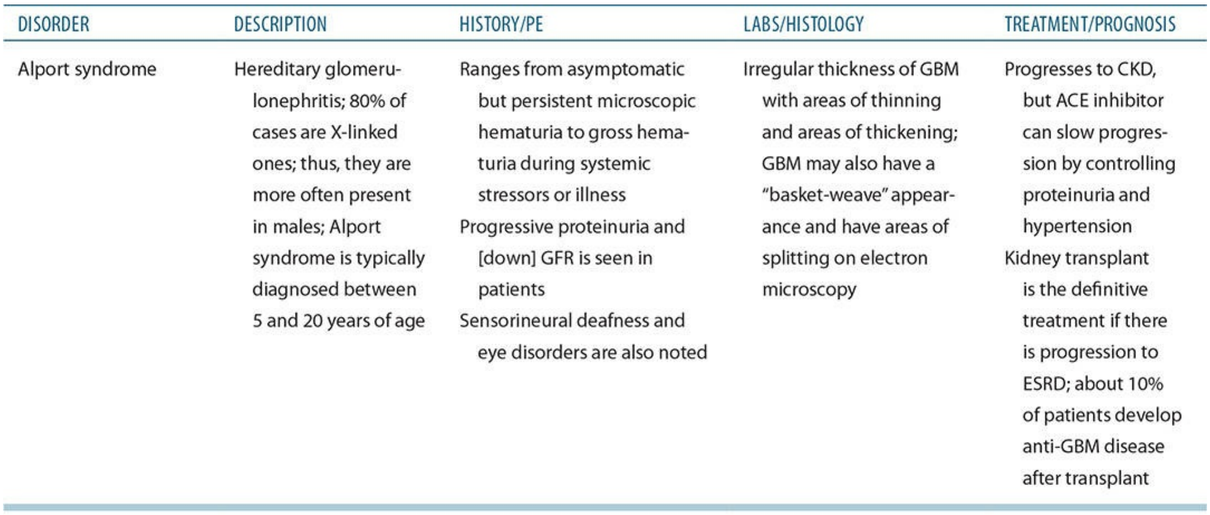
NEPHRITIC SYNDROME

A disorder of glomerular inflammation, also called glomerulonephritis. Proteinuria may be present but is variable. If severe glomerular inflammation, it can exceed 2 g/day and lead to a concurrent nephrotic syndrome. Most cases of glomerulonephritis are usually associated with less proteinuria, often <1.5 g/day. Causes are summarized in Table 2.15-5. Subtypes based on serum complement levels are displayed in Figure 2.15-9.

TABLE 2.15-5. **Causes of Nephritic Syndrome**

DISORDER	DESCRIPTION	HISTORY/PE	LABS/HISTOLOGY	TREATMENT/PROGNOSIS
IMMUNE COMPLEX				
Postinfectious glomerulonephritis	Classically associated with recent group A β-hemolytic streptococcal infection but can be seen with many other infections (usually 2–4 weeks after the infectious trigger) Most common cause in children	Tea- or cola-colored urine, HTN, edema, and occasional oliguria	Low serum C3 that normalizes 6–8 weeks after presentation; ASO and/or anti-DNase B (if *Streptococcus* associated); lumpy-bumpy immunofluorescence	Supportive with diuretics to treat fluid overload and/or HTN, most patients have a complete recovery
IgA nephropathy (Berger disease)	Most common cause of glomerulonephritis in adults; typically occurs concurrent with an upper respiratory or GI infection (IgA-producing mucosa); this is the renal manifestation of HSP (IgA vasculitis)	Episodic gross hematuria with respiratory and/or GI infections; often with persistent microscopic hematuria between infections; patient may also have chronic HTN and low to moderate levels of proteinuria HSP is diagnosed when there is palpable purpura without thrombocytopenia and one of the following three: renal disease, arthralgia, abdominal pain	Normal C3; IgA deposits on immunofluorescence	ACE inhibitors in patients with persistent hypertension and/or proteinuria; glucocorticoids in select severe inflammatory presentations Nonresponsive patients have slow progression to ESRD Treatment for HSP in the absence of renal involvement is generally supportive
Membranoproliferative nephropathy type I/III (nomenclature is changing, but these are the classic terms, based on electron microscopy)	Immune complex–mediated MPGN either primary (especially in children) or secondary to HBV, HCV, SLE, or cryoglobulinemia	May present with nephrotic syndrome; clinical features may include gross hematuria, HTN, and/or edema	"Tram-track," double-layered basement membrane; subendothelial and mesangial deposits are present	Prednisone ± immunosuppressive therapy the mainstays of treatment; RAAS inhibition is often given
Membranoproliferative nephropathy type II (nomenclature is changing, but this is the classic term based on electron microscopy)	Complement-mediated MPGN (dense deposit disease) associated with C3 nephritic factor and persistent compliment activation with ↓ C3 levels	This nephritis may also present with a nephrotic syndrome; clinical features may include gross hematuria, hypertension, and/or edema	Intramembranous dense deposits. "Tram-track," double-layered basement membrane may also be present (arrows in image) 	Antihypertensive therapy and RAAS inhibition; severe cases call for immunosuppressive therapy

DISORDER	DESCRIPTION	HISTORY/PE	LABS/HISTOLOGY	TREATMENT/PROGNOSIS
Lupus nephritis	Classified as WHO types I–VI; the severity of renal disease often determines overall prognosis	May present with gross hematuria, HTN, and/or edema, or as microscopic proteinuria/hematuria; renal disease may include nephrotic (membranous), RPGN, nephritic (membranoproliferative), or mixed presentations	Mesangial proliferation; subendothelial and/or subepithelial immune complex deposition; there is typically a low serum C3 and C4 level	Prednisone and immunosuppressive therapy (mycophenolate, cyclophosphamide) the mainstays of treatment; RAAS inhibition is also often given
PAUCI-IMMUNE (NO IG DEPOSITS ON IMMUNOFLUORESCENCE)				
Granulomatosis with polyangiitis ([GPA], formerly Wegener granulomatosis)	Granulomatous inflammation of the respiratory tract (with nasopharyngeal involvement) and kidney with necrotizing vasculitis of glomerular capillaries	Nasopharyngeal symptoms that may include stridor; cavitary pulmonary lesions bleed and lead to hemoptysis; renal manifestations often include AKI/RPGN, HTN, gross hematuria, and oliguria	Presence of PR3-ANCA/c-ANCA (antiproteinase 3); crescents may be apparent on light microscopy	High-dose corticosteroids, cyclophosphamide, or rituximab; patients tend to have frequent relapses; life-threatening cases are treated with plasmapheresis
Microscopic polyangiitis	Small vessel vasculitis similar to GPA; no granulomas	Similar to GPA but no nasopharyngeal involvement; renal manifestation often AKI, HTN, sometimes gross hematuria, oliguria	MPO-ANCA/p-ANCA (antimyeloperoxidase); necrotizing glomerulonephritis with crescents on light microscopy	Glucocorticoids, cyclophosphamide, or rituximab; life-threatening cases are treated with plasmapheresis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Small vessel vasculitis similar to GPA	Asthma, sinusitis, skin nodules/purpura, peripheral neuropathy; renal manifestation often AKI, HTN, sometimes gross hematuria, oliguria	MPO-ANCA, eosinophils, IgE; necrotizing glomerulonephritis with crescents on light microscopy	Glucocorticoids, cyclophosphamide, or rituximab; life-threatening cases are treated with plasmapheresis
ANTI–GLOMERULAR BASEMENT MEMBRANE (GBM) DISEASE				
Goodpasture syndrome	Rapidly progressing glomerulonephritis with pulmonary hemorrhage; peak incidence affects males in their mid-20s	Hemoptysis, dyspnea, possible respiratory failure; no upper respiratory tract involvement; renal manifestations often include AKI/RPGN, HTN, gross hematuria, oliguria	Linear anti-GBM IgG deposits on immunofluorescence; iron-deficiency anemia; hemosiderin-filled macrophages in sputum; pulmonary infiltrates on CXR; necrotizing glomerulonephritis with crescents apparent via light microscopy	Plasma exchange therapy; pulsed steroids and cyclophosphamide Anti-GBM disease is severe and life-threatening; it may not be responsive to treatment and may progress to ESRD



DISORDER	DESCRIPTION	HISTORY/PE	LABS/HISTOLOGY	TREATMENT/PROGNOSIS
Alport syndrome	Hereditary glomerulonephritis; 80% of cases are X-linked ones; thus, they are more often present in males; Alport syndrome is typically diagnosed between 5 and 20 years of age	Ranges from asymptomatic but persistent microscopic hematuria to gross hematuria during systemic stressors or illness Progressive proteinuria and [down] GFR is seen in patients Sensorineural deafness and eye disorders are also noted	Irregular thickness of GBM with areas of thinning and areas of thickening; GBM may also have a "basket-weave" appearance and have areas of splitting on electron microscopy	Progresses to CKD, but ACE inhibitor can slow progression by controlling proteinuria and hypertension Kidney transplant is the definitive treatment if there is progression to ESRD; about 10% of patients develop anti-GBM disease after transplant

AKI, Acute kidney injury; *ANCA,* antineutrophil cytoplasmic antibody; *Anti-DNase B,* anti–deoxyribonuclease B; *ASO,* antistreptolysin O; *CXR,* x-ray of the chest; *HBV,* Hepatitis B virus; *HCV,* Hepatitis C virus; *HSP,* Henoch-Schonlein purpura; *HTN,* hypertension; *MPGN,* membranoproliferative glomerulonephritis; *PR3,* proteinase 3; *RPGN,* rapidly progressive glomerulonephritis; *SLE,* systemic lupus erythematosus; *WHO,* World Health Organization. (Image reproduced with permission from USMLE-Rx.com; courtesy of Dr. Adam Weinstein.)

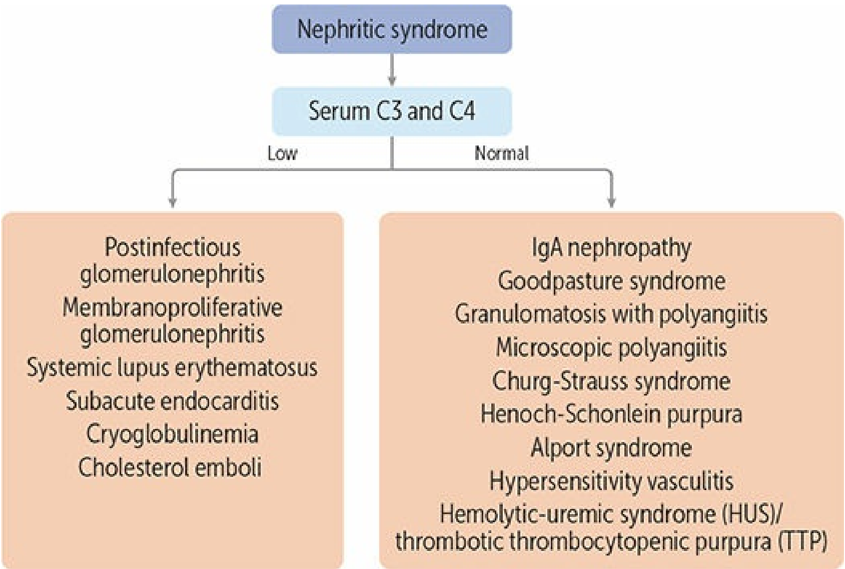

Nephritic syndrome
Serum C3 and C4
Low
Normal
Postinfectious glomerulonephritis
Membranoproliferative glomerulonephritis
Systemic lupus erythematosus
Subacute endocarditis
Cryoglobulinemia
Cholesterol emboli
IgA nephropathy
Goodpasture syndrome
Granulomatosis with polyangiitis
Microscopic polyangiitis
Churg-Strauss syndrome
Henoch-Schonlein purpura
Alport syndrome
Hypersensitivity vasculitis
Hemolytic-uremic syndrome (HUS)/
thrombotic thrombocytopenic purpura (TTP)

FIGURE 2.15-9. **Serum complement levels in nephritic syndromes.** (Reproduced with permission from USMLE-Rx.com.)

KEY FACT

Postinfectious glomerulonephritis will present 2 to 6 weeks after an infection and has a low C3; IgA nephropathy will present concurrent with an infection and has a normal C3.

KEY FACT

Granulomatosis with polyangiitis = kidney + lung + sinus
Microscopic polyangiitis = kidney + lung
Churg-Strauss syndrome = kidney + asthma

History/PE

The classic findings of nephritic syndrome may include microscopic or macroscopic (if so, tea- or cola-colored urine), hypertension, and/or edema.

Diagnosis

- Urinalysis (UA) shows hematuria and variable degrees of proteinuria.
- In most severe cases, patients may have a ↓ GFR with elevated BUN and creatinine. See Table 2.15-5 for pertinent labs.
- Renal biopsy may be needed for histologic evaluation and treatment and prognosis considerations.
- Two specific examples of findings are shown in Figure 2.15-10.

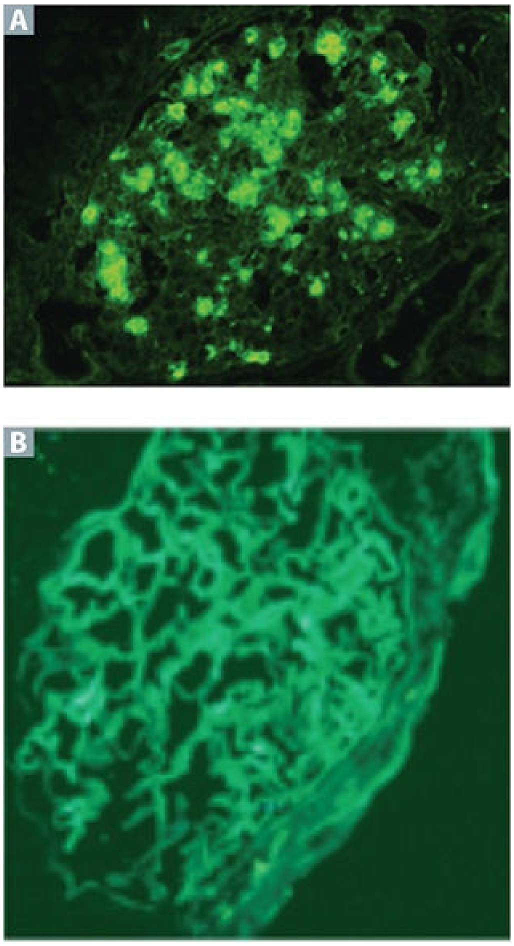


FIGURE 2.15-10. **Examples of immunofluorescent findings in nephritic syndrome. (A)** Granular endocapillary immune complex deposition, causing "lumpy-bumpy" texture, also known as "starry sky" immunofluorescence, found in postinfectious glomerulonephritis. **(B)** Linear immunofluorescence seen in Goodpasture syndrome. (Image A reproduced with permission from Oda T, Yoshizawa N, Yamakami K, et al. The role of nephritis-associated plasmin receptor [NAPLR] in glomerulonephritis associated with streptococcal infection, *Biomed Biotechnol.* 2012;2012:417675. Image B reproduced with permission from Kasper D et al. *Harrison's Principles of Internal Medicine,* 19th ed. New York, NY: McGraw-Hill; 2015.)

Treatment

- If present, treat hypertension, fluid overload with salt restriction, RAAS blockade, ± diuretics.
- In some cases, depending on the etiology, corticosteroids ± other immunosuppressant agents are a necessary treatment to reduce glomerular inflammation.

NEPHROTIC SYNDROME

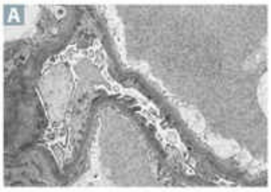
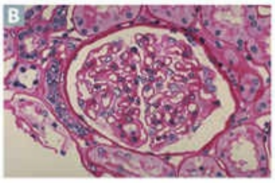
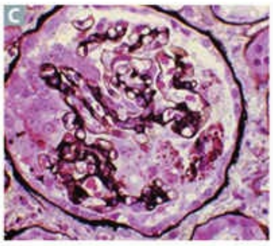
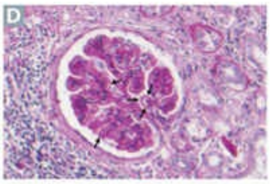
Nephrotic syndrome is defined as follows:

- Hyperproteinuria (≥3.5 g/day)
- Hypoproteinemia/hypoalbuminemia—albumin levels fall because of protein loss
- Hyperlipidemia (may result in accelerated atherosclerosis if chronic)
- Edema

Nephrotic syndrome can cause a hypercoagulable state with thrombosis due to loss of antithrombin III, protein C, and protein S in urine.

Approximately one third of all cases result from systemic diseases such as DM, systemic lupus erythematosus (SLE), or amyloidosis. In children, the most common cause is minimal change disease, a primary disease of the kidney and not a systemic disease. Causes and findings are summarized in Table 2.15-6.

TABLE 2.15-6. Causes of Nephrotic Syndrome

DISORDER	DESCRIPTION	HISTORY/PE	LABS/HISTOLOGY	TREATMENT/PROGNOSIS
Minimal change disease  	The most common cause of nephrotic syndrome in children Idiopathic etiology; secondary causes include NSAIDs and hematologic malignancies (eg, Hodgkin disease)	Sudden onset of edema	Biopsy is recommended in treatment-resistant disease or with age >12 years; otherwise diagnosis is clinical; light microscopy appears normal; electron microscopy shows diffuse effacement of epithelial foot processes (see Image A) Image B shows a normal glomerulus	Steroids; favorable prognosis
Focal segmental glomerulosclerosis (FSGS) 	Idiopathic, but also can be secondary to IV drug use (heroin), HIV, sickle cell disease, and obesity; focal segmental glomerulosclerosis is the most common cause of nephrotic syndromes in adults, especially in people of African descent	Presents with hypertension and often with edema	Biopsy shows focal glomerular sclerosis in capillary tufts (see Image C)	For idiopathic FSGS, treatment is prednisone and/or other immunosuppressant therapy; in addition, and for all other cases, supportive treatments with ACE inhibitors/ARBs to ↓ proteinuria and treat hypertension
Membranous nephropathy 	Accounts for ±30% of nephrotic syndromes in adults; membranous nephropathy is the most common cause of nephrotic syndrome in people of European descent	May be primary (antibodies to phospholipase [PLA]2 receptors) or secondary to solid tumor malignancies, infections (HBV, malaria), autoimmune diseases (SLE), drugs (NSAIDs, gold) Patients present with anasarca Membranous nephropathy has the highest rate of thrombosis, likely related to severity of protein losses	"Spike-and-dome" appearance caused by granular deposits of IgG and C3 at the subepithelial side of the basement membrane; on light microscopy, GBM thickening is seen (*arrows* in Image D) Antiphospholipase A_2 receptor (PLA2R) antibodies are associated with primary membranous nephropathy	RAAS inhibition is first line; prednisone and immunosuppressive therapy are for severe disease refractory to RAAS inhibition alone

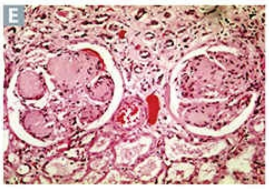
DISORDER	DESCRIPTION	HISTORY/PE	LABS/HISTOLOGY	TREATMENT/PROGNOSIS 8P5.5
Diabetic nephropathy 	Has two characteristic forms: diffuse hyalinization and nodular glomerulosclerosis (Kimmelstiel-Wilson lesions)	Patients generally have long-standing, poorly controlled DM with evidence of other organ system complications (eg, retinopathy, neuropathy); rapidly progressing kidney disease is suggestive of a different etiology	Thickened GBM; mesangial matrix; Kimmelstiel-Wilson lesions are seen (see Image E)	Tight control of blood sugar; administration of ACE inhibitors or ARBs The physician can screen for diabetic nephropathy with random urine microalbumin/creatinine ratio
Renal amyloidosis	Primary (plasma cell dyscrasia) and secondary (infectious or inflammatory)—the most common	Patients may have multiple myeloma or a chronic inflammatory disease (eg, rheumatoid arthritis, TB)	Nodular glomerulosclerosis; electron microscope reveals amyloid fibrils, apple-green birefringence with Congo red stain	Prednisone and melphalan; bone marrow transplantation may be used for multiple myeloma; AA amyloidosis is managed by treating the underlying inflammatory condition

Image A reproduced with permission from Teoh DC, El-Modir A. Managing a locally advanced malignant thymoma complicated by nephrotic syndrome: a case report. *J Med Case Rep.* 2008;2:89 doi:10.1186/1752-1947-2-89. Image B and C reproduced with permission from Ramidi GB, Kurukumbi MK, Sealy PL. Collapsing glomerulopathy in sickle cell disease: a case report. *J Med Case Rep.* 2011;5:71 doi:10.1186/1752-1947-5-71. Image C reproduced with permission from Ramidi GB, Kurukumbi MK, Sealy PL. Collapsing glomerulopathy in sickle cell disease: a case report. *J Med Case Rep.* 2011;5:71 doi:10.1186/1752-1947-5-71. Image D reproduced with permission from USMLE-Rx.com. Image E reproduced with permission from the US Department of Health and Human Services and Dr. Edwin P. Ewing, Jr.

KEY FACT

Differential diagnosis for nephritic/nephrotic syndrome with low C3: Postinfectious, membranoproliferative glomerulonephritis (including mixed cryoglobulinemia) and lupus nephritis.

History/PE

- Presents with generalized edema. Sometimes patients will notice they have foamy urine. In severe cases, dyspnea and ascites and other complications from anasarca may develop.
- Patients have ↑ susceptibility to infection (caused by loss of IgG protein in the urine) and hypercoagulable states with an ↑ risk for venous thrombosis and pulmonary embolism (caused by loss of antithrombin 3, increased platelet aggregation, and changes in protein C and S levels). This increased risk of hypercoagulability commonly manifests as renal vein thrombosis.

KEY FACT

Mixed cryoglobulinemia presents with palpable purpura, arthralgias, nephritic/nephrotic syndrome, low C3, and positive hepatitis C virus (HCV).

Diagnosis

- UA shows proteinuria (≥3.5 g/day) and may show lipiduria (Maltese crosses signifying lipids on microscopic urine exam). It is now more common for clinicians to use a spot protein-to-creatinine ratio rather than 24-hour urine. The cutoff for nephrotic syndrome is 2.0 on this ratio.
- Blood chemistry shows ↓ albumin (<3 g/dL) and hyperlipidemia.
- Evaluation should include workup for secondary causes.
- Renal biopsy may also be needed to definitively diagnose the underlying etiology.

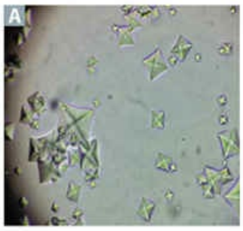
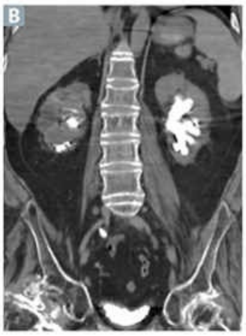
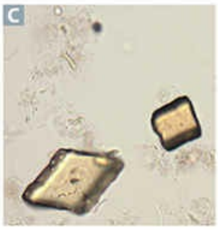
Treatment

- Treat with salt restriction and judicious diuretic therapy.
- If the patient is hypertensive, the physician can use RAAS blockade and/or diuretic therapy.
- If nephrotic syndrome is chronic, the physician may need to treat the patient with statins. A history of or a suspicion for thrombosis calls for anticoagulants.
- Steroids and/or other immunosuppressant medications may be useful for certain etiologies.
- ACE inhibitors/ARBs ↓ proteinuria and diminish the progression of renal disease in patients with renal scarring (especially in patients with diabetes).
- Vaccinate patients with 23-polyvalent pneumococcus vaccine (PPV23), as patients are at ↑ risk for *Streptococcus pneumoniae* infection, based on hypogammaglobulinemia from immunoglobulin losses in urine and edema (pulmonary edema, ascites).

NEPHROLITHIASIS

Renal calculi. Stones are most commonly calcium oxalate, but many other types exist (see Table 2.15-7). Risk factors include a ⊕ family history, low fluid intake, gout, medications (allopurinol, chemotherapy, loop diuretics), postcolectomy/postileostomy, specific enzyme deficiencies, type I RTA (caused by alkaline urinary pH and associated hypocitraturia), and hyperparathyroidism.

TABLE 2.15-7. Types of Nephrolithiasis

TYPE	ETIOLOGY AND CHARACTERISTICS	URINARY PH	TREATMENT
Calcium oxalate  	Most common causes are idiopathic hypercalciuria, but also may see in fat malabsorption (eg, with Crohn disease or bowel resection) Stones are radiopaque Envelope- or dumbbell-shaped stones (Image A)	Calcium oxalate precipitates with hypocitraturia, which is often associated with ↓ pH	Hydration, dietary sodium restriction, thiazide diuretic Do not decrease calcium intake (can lead to hyperoxaluria and risk for osteoporosis) May also begin citrate supplements, but pH must not be raised too high
Calcium phosphate	Most common causes are idiopathic hypercalciuria but also may see in primary hyperparathyroidism or immobility syndromes that result in high bone loss Stones are radiopaque Wedge-shaped prism stones	Calcium phosphate precipitates at ↑ pH	Hydration, dietary sodium restriction Thiazide diuretic only for idiopathic etiology and not when hyperparathyroidism is etiology Do not decrease calcium intake (can lead to hyperoxaluria and risk for osteoporosis)
Struvite ($MgNH_4PO_4$) or "triple phosphate"  	Associated with urease-producing organisms (eg, *Proteus*) Patients may have history of recurrent UTIs Stones are radiopaque Staghorn-shaped stones (Image B) Frequency: 9%	↑ pH	Hydration Treat UTI if present Surgically remove staghorn stones (antibiotics alone are not enough)
Uric acid  	Associated with gout, xanthine oxidase deficiency, and high purine turnover states (eg, chemotherapy) Stones are radiolucent on plain film, but can be detectable with CT (not as bright as calcium stones on CT) Rhomboid-shaped stones (Image C) Frequency: 7%	↓ pH	Hydration Alkalize urine First-line management: Restrict dietary purines If stones recur despite dietary management, consider allopurinol

TYPE	ETIOLOGY AND CHARACTERISTICS	URINARY PH	TREATMENT
Cystine	Caused by a defect in renal transport of certain amino acids (**COLA**: **C**ystine, **O**rnithine, **L**ysine, and **A**rginine) Stones are partially radiopaque (may need CT to see; not always seen on x-ray) Hexagonal crystals Frequency: 1%	↓ pH	Hydration, dietary sodium restriction Alkanize urine If stones recur despite above treatments, consider penicillamine or tiopronin

Image A reproduced with permission from Nair S, George J, Kumar S, Gracious N. Acute oxalate nephropathy following Ingestion of Averrhoa bilimbi Juice. *Case Rep Nephrol.* 2014;2014:240936. doi: 10.1155/2014/240936. Image B reproduced with permission from USMLE-Rx.com. Image C courtesy of Dr. Adam Weinstein.

KEY FACT

The bacteria associated with “staghorn calculi” are urease-producing organisms, such as *Proteus* and *Klebsiella*.

History/PE

- Presents with acute onset of severe, colicky flank pain that may radiate to the groin and is associated with nausea and vomiting.
- Patients are unable to get comfortable and shift position frequently (as opposed to those with peritonitis, who lie still).

Diagnosis

- UA may show gross or microscopic hematuria (85%).
- Noncontrast abdominal CT scan is the **gold standard** for the diagnosis of kidney stones (see Fig. 2.15-11).

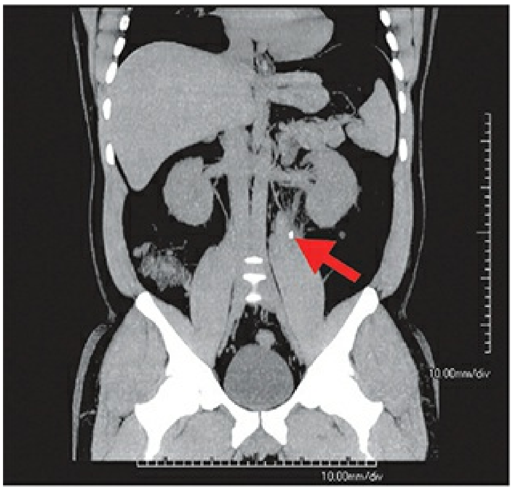


FIGURE 2.15-11. Nephrolithiasis. CT scan shows a dense 1-cm calcification *(arrow)* in the left ureter, consistent with nephrolithiasis. (Reproduced with permission from Tintinalli JE et al. *Tintinalli’s* Emergency Medicine: A Comprehensive Study Guide, 7th ed. New York, NY: McGraw-Hill; 2011.)

- Ultrasound is preferred for pregnant patients and children when there is a low likelihood for another pathology.
- Plain x-rays of the abdomen are still useful for following the progression/treatment of

larger stones.

KEY FACT

In gout, urate crystals are needle shaped. In contrast, uric acid nephroliths are pleomorphic.

Treatment

- **Best initial treatment:** Hydration and analgesia (see Fig. 2.15-12).

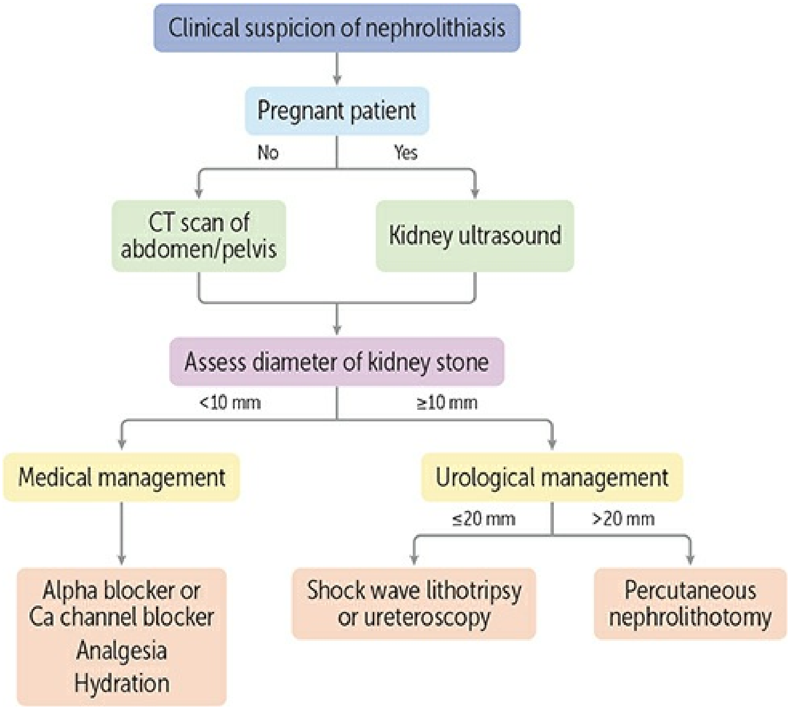

Clinical suspicion of nephrolithiasis
Pregnant patient
No
Yes
CT scan of abdomen/pelvis
Kidney ultrasound
Assess diameter of kidney stone
<10 mm
≥10 mm
Medical management
Urological management
≤20 mm
>20 mm
Alpha blocker or Ca channel blocker
Analgesia
Hydration
Shock wave lithotripsy or ureteroscopy
Percutaneous nephrolithotomy

FIGURE 2.15-12. **Nephrolithiasis treatment algorithm.** (Reproduced with permission from USMLE-Rx.com.)

- α_1-Receptor blockers (eg, tamsulosin) and calcium channel blockers (eg, nifedipine) reduce ureteral spasms and facilitate passage of ureteral stone <10 mm, reducing the need for analgesics.
- Treatment varies according to the size and diameter of the stone:
  - <5 mm: May pass spontaneously
  - <10 mm: Higher rate of spontaneous passage with α-blocker or calcium channel blocker therapy
  - <5 to 20 mm: May be treated with shock wave lithotripsy or ureteroscopy
  - >20 mm: Percutaneous nephrolithotomy
- Dietary changes to prevent calcium stones include ↑ fluid intake (most important), normal calcium intake (recommended daily allowance [RDA]), and ↓ sodium intake. If caused by hyperoxaluria, then ↓ oxalate intake.
- Indications for a urologic consult: Stone size >9 mm, refractory pain/vomiting, signs of sepsis or complete obstruction

POLYCYSTIC KIDNEY DISEASE

Characterized by the presence of progressive cystic dilation of the renal tubules. Polycystic kidney disease includes two main types—ADPKD and ARPKD.

- **Autosomal dominant polycystic kidney disease (ADPKD):**
  - Most common
  - Usually asymptomatic until patients are >30 years of age (as cysts gradually enlarge with time), although about 10% of these patients present in childhood
  - Possible formation in other organs, especially the liver, pancreas, spleen, and epididymis
  - In one half of ADPKD patients, ESRD to require dialysis by 60 years of age; other patients may simply have mildly reduced renal function and only require supportive care and BP control
- **Autosomal recessive polycystic kidney disease (ARPKD):**
  - Less common but more severe
  - Presents in infants and young children with renal failure, liver fibrosis, and portal hypertension; ARPKD can lead to death in the first few days of life if associated with in utero oliguria (oligohydramnios) leading to Potter sequence

KEY FACT

If a patient with known ADPKD develops a sudden-onset, severe headache, rule out subarachnoid hemorrhage from a ruptured berry aneurysm!

History/PE

- **ADPKD:**
  - Presenting symptoms are hypertension, bilateral palpable abdominal masses, flank pain, history of UTI or gross hematuria. Polyuria and nocturia can also be seen. Sharp, localized pain may result from cyst rupture, infection, or passage of renal calculi.
  - Additional findings include hepatic/pancreatic cysts, cerebral berry aneurysms (especially in patients with ⊕ family history; risk also increases with age), valvular heart disease (mitral valve prolapse [MVP] and aortic regurgitation [AR]), colonic diverticula, and abdominal and inguinal hernia.
- **ARPKD:** Hypertension, abdominal distention, and flank masses are the most common presenting findings. It is most commonly identified prenatally.
- **ADPKD and ARPKD:**
  - Patients may have large, palpable kidneys on abdominal examination.
  - A single, simple renal cyst in an adult does not suggest ADPKD and does not require further evaluation.

Q

A 19-year-old man with a history of recurrent kidney stones presents with acute left flank pain. His father also has a history of kidney stones. A urinary cyanide nitroprusside test is ⊕. A CT scan confirms nephrolithiasis. What is the most likely diagnosis?

Diagnosis

Based on ultrasonography (most common) or CT scan (see Fig. 2.15-13). Multiple bilateral cysts will be present throughout the renal parenchyma, and renal enlargement will be visualized. Genetic testing for ADPKD (*PKD1* and *PKD2* genes) and ARPKD (*PKHD* gene) is available but often not necessary. Patients >18 years of age with + family history may be offered a screening ultrasound.

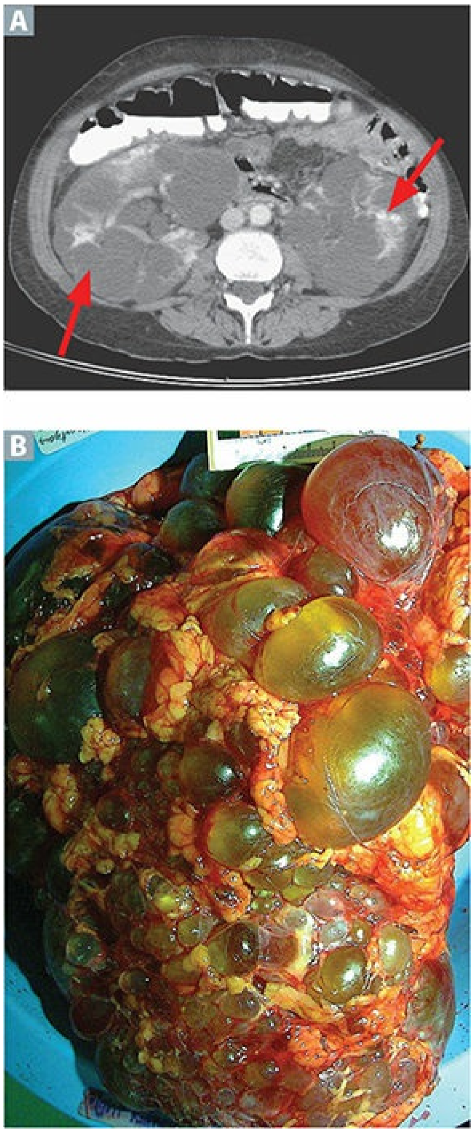


FIGURE 2.15-13. **Autosomal dominant polycystic kidney disease. (A)** Contrast-enhanced CT scan demonstrates bilaterally enlarged kidneys that have been almost entirely replaced by cysts *(arrows).* **(B)** Gross specimen of a right kidney from a patient with ADPKD who underwent renal transplantation. (Image A adapted with permission from Fauci AS et al. *Harrison's Principles of Internal Medicine,* 17th ed. New York, NY: McGraw-Hill; 2008. Image B reproduced with permission from USMLE-Rx.com.)

Treatment

- Prevent complications and ↓ the rate of progression to ESRD. Early management of urinary tract infections (UTIs) is critical to prevent renal cyst infection. BP control (ACE inhibitors, ARBs) is necessary to ↓ hypertension-induced renal damage and control proteinuria. Sodium intake should also be limited. Aggressive lipid control with statin to decrease CV risk.
- Dialysis and renal transplantation are used to manage patients with ESRD.
- High fluid intake is helpful to prevent development of kidney stones and may be helpful at

slowing cyst progression too (ADH stimulates cyst growth). Vasopressin receptor antagonists have also been approved for use.

HYDRONEPHROSIS

Dilation of the urinary tract—often secondary to downstream obstruction of the urinary tract. In pediatric patients, the obstruction is often at the ureteropelvic junction but may also be at the ureterovesicular junction (at the insertion into the bladder) or at the bladder outlet (eg from “posterior urethral valves”). In adults, it may be caused by benign prostatic hyperplasia (BPH) and aortic aneurysms. In both children and adults, it may be from neurogenic bladder (spinal cord injuries), tumors, or renal calculi. Apart from obstruction, hydronephrosis can also be caused by excessively high-output urinary flow and vesicoureteral reflux.

History/PE

May be asymptomatic or may present with flank/back pain, abdominal pain, and/or UTIs.

KEY FACT

Left untreated, hydronephrosis resulting from urinary obstruction poses a risk for infection and sepsis, as well as kidney damage with resulting hypertension, acute kidney injury, and/or chronic kidney disease.

Diagnosis

Ultrasonography or CT scan to detect dilation of the renal pelvis, calyces (see Fig. 2.15-14A), and/or ureter.

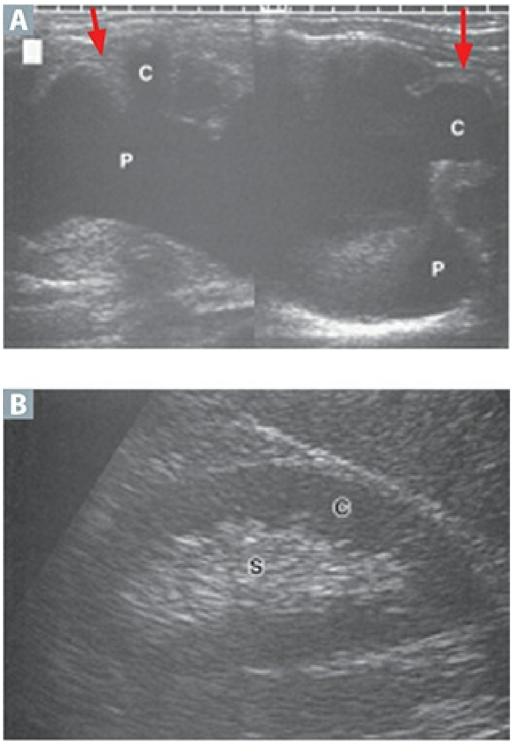


FIGURE 2.15-14. **Hydronephrosis. (A)** Ultrasound of a renal transplant shows severe hydronephrosis, with dilation of the renal pelvis *(P)* and the renal calyces *(C)*. The overlying

renal cortex is severely thinned *(arrows)*. **(B)** Normal renal ultrasound for comparison. *C*, cortex; *S*, sinus fat. (Reproduced with permission from Tanagho EA, McAninch JW. *Smith's General Urology*, 17th ed. New York, NY: McGraw-Hill; 2008.)

Treatment

- Some pediatric cases will spontaneously resolve. Otherwise, the only treatment is to surgically correct any anatomic obstruction or reflux; if the patient has a neurogenic bladder, the physician can start a clean intermittent catheterization regimen for bladder emptying.
- Ureteral stent placement across the obstructed area of the urinary tract and/or percutaneous nephrostomy tube placement to relieve pressure may be appropriate if the urinary outflow tract is not sufficiently cleared of obstruction. Foley or suprapubic catheters may be required for lower urinary tract obstruction (eg, BPH).

A

Cystinuria is the most likely diagnosis. It refers to decreased cystine reabsorption caused by a defect in proximal tubular amino acid transport. Hexagonal crystals probably would be visible on UA.

SCROTAL PAIN AND SWELLING

Scrotal wall swelling can be seen in generalized edematous states (nephrotic syndrome, liver disease, congestive heart failure) or in angioedema or allergic reactions.

Etiologies of a swollen/enlarged scrotum can be broken down as follows (see Fig. 2.15-15):

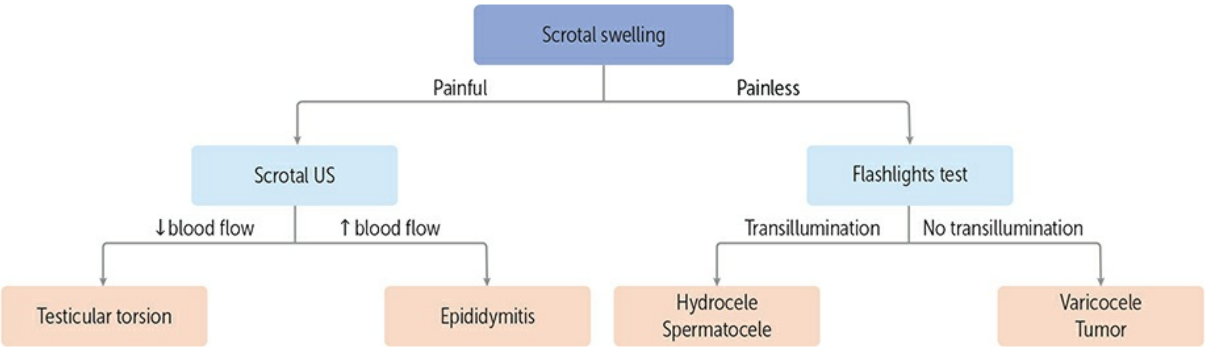


FIGURE 2.15-15. Evaluation of scrotal swelling. (Reproduced with permission from USMLE-Rx.com.)

- Painless etiologies → hydrocele (remnant of processus vaginalis; may be accompanied by inguinal hernia), varicocele (dilatation of pampiniform plexus), tumors
- Painful etiologies → epididymitis, orchitis, testicular torsion (twisting and subsequent ischemia of the spermatic cord), incarcerated inguinal hernias

Prostatitis (both acute and chronic), distally migrated ureteral stones, and chronic pelvic pain syndrome can manifest as scrotal pain.

History/PE

Detailed history regarding preceding viral infections, UTIs, sexual activity, and acuity of onset of swelling and/or pain should be obtained. Testicular torsion tends to present very acutely with severe pain that can lead to nausea/emesis, whereas other etiologies present more gradually.

Physical examination can reveal a number of characteristic features:

- Hydrocele can present with a transilluminating scrotum. Increase of size during Valsalva maneuver could indicate communicating hydrocele.
- Varicocele does not transilluminate. It is often described as having a “bag of worms” texture to palpation, and more commonly it is seen in the left testicle (see Fig. 2.15-16). Varicoceles can also augment with the Valsalva maneuver.

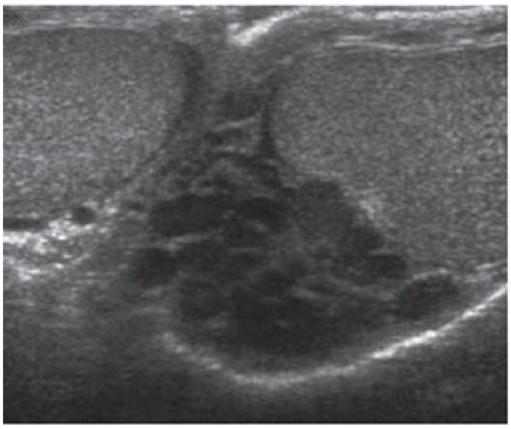


FIGURE 2.16-16. **Varicocele.** Multiple tortuous tubular like structures are seen in the left scrotum. (Reproduced with permission from Mak CW, Tzeng WS. Sonography of the scrotum. Available at https://www.intechopen.com/chapters/27883.)

- Epididymitis can present with a ⊕ Prehn sign (↓ pain with scrotal elevation); ⊖ Prehn sign is manifested in torsion.

Diagnosis

- If the diagnosis is unclear after physical examination, an ultrasound should be pursued. Doppler ultrasonography shows normal to ↑ blood flow to testes in epididymitis and ↓ blood flow in torsion.
- UA and culture may show *Neisseria gonorrhoeae, Escherichia coli,* or *Chlamydia* in epididymitis. Culture is required to direct therapy in acute prostatitis, which may accompany epididymitis. Chronic prostatitis/chronic pelvic pain syndrome will present with culture ⊖ irritation on voiding.

KEY FACT

A tender, boggy prostate on rectal examination in the setting of fever is diagnostic for prostatitis.

Treatment

- **Hydrocele:** Typically resolves within 12 months. Hydroceles that do not resolve should be removed surgically because of risk for inguinal hernia.
- **Varicocele:** May need surgery if large or symptomatic.
- **Epididymitis and acute prostatitis:** Antibiotics (ceftriaxone, doxycycline, fluoroquinolones); NSAIDs; scrotal support for pain.
- **Testicular torsion:** Immediate surgery (<6 hours) to salvage testis. The physician should

attempt manual detorsion only if surgery is unavailable or if it will not delay surgery. Orchiopexy of both testes to prevent future torsion.

- **Chronic prostatitis/chronic pelvic pain syndrome:** α-Blockers, 5-α-reductase inhibitors.

URINARY INCONTINENCE

The involuntary loss of urine caused by either bladder or urethral sphincter dysfunction.

History/PE

Table 2.15-8 outlines the types of incontinence along with their distinguishing features and treatment (see also the **DIAPPERS** mnemonic).

TABLE 2.15-8. **Types of Incontinence**

TYPE	HISTORY OF URINE LOSS	MECHANISM	TREATMENT
Total	Uncontrolled loss at all times and in all positions	Loss of sphincteric efficiency (previous surgery, nerve damage, cancer infiltration) Abnormal connection between the urinary tract and the skin (fistula)	Surgery
Stress	Loss following rise in intra-abdominal pressure (coughing, sneezing, lifting)	Urethral sphincteric insufficiency caused by laxity of pelvic floor musculature Common in multiparous women or after pelvic surgery	Kegel exercises and pessary Urethral sling procedure
Urge	Strong, unexpected urge to void that is unrelated to position or activity	Can be seen in bladder outlet obstruction (BPH, drugs that increase sphincter tone) or detrusor overactivity	Pelvic floor exercises, bladder training Pharmacologic interventions: Anticholinergics (first line), β-agonists such as mirabegron (second line)
Overflow	Dribbling experienced after incomplete emptying of bladder	Chronically distended bladder with intravesical pressure that just exceeds the outlet resistance, allowing a small amount of urine to dribble out	Placement of urethral catheter in acute settings Treatment of underlying diseases Timed voiding/catheterization

Neurologic injuries can lead to several/mixed types of incontinence (eg, detrusor overactivity after stroke, stress incontinence, or overflow incontinence after spinal cord injury).

MNEMONIC

Causes of urinary incontinence without specific urogenital pathology— **DIAPPERS**

Delirium/confusion
Infection
Atrophic urethritis/vaginitis
Pharmaceutical
Psychiatric disorders (especially depression)
Excessive urinary output (hyperglycemia, hypercalcemia)
Restricted mobility
Stool impaction

Diagnosis/Treatment

- A UA can evaluate for pyuria that might suggest a UTI. Assessing serum creatinine can reveal signs of renal dysfunction if urinary obstruction leading to overflow is suspected.
- Voiding diaries may be helpful in better defining the type of incontinence.
- Urodynamic and radiographic testing is not routinely done for evaluation of incontinence. These measures merit consideration if plans exist for surgical management of incontinence.
- Table 2.15-8 outlines treatment options according to subtype.

INTERSTITIAL CYSTITIS (PAINFUL BLADDER SYNDROME)

Chronic, painful bladder condition that is associated with psychiatric disorders, other pain syndromes (eg, fibromyalgia, irritable bowel syndrome [IBS]), and a history of UTIs. The onset is gradual. Pain exacerbated by bladder filling, exercise, sexual intercourse, alcohol consumption, and prolonged sitting. Pain is relieved with voiding. Interstitial cystitis is more common in females.

History/PE

- Lower urinary tract symptoms
- UA normal
- Symptoms for >6 weeks

Diagnosis

Primarily clinical.

Treatment

- Avoiding triggers (behavioral modification) first line
- Physical therapy, analgesics
- Amitriptyline for refractory symptoms

ERECTILE DYSFUNCTION

Found in 10% to 25% of middle-aged and older adult males. Classified as failure to initiate (eg, psychologic, endocrinologic, neurologic), failure to fill (eg, arteriogenic), or failure to store (eg, veno-occlusive dysfunction). Risk factors include DM, atherosclerosis, medications (eg, β-blockers, selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants [TCAs], diuretics), hypertension, heart disease, surgery or radiation for prostate cancer, and spinal cord injury.

History/PE

- Ask about risk factors (diabetes, peripheral vascular disease), medication use, recent life changes, and psychologic stressors.
- The distinction between psychologic and organic erectile dysfunction (ED) is based on situational dependence (eg, occurring with only one partner) and the presence of nocturnal or early-morning erections with penile tumescence testing (if present, it is nonorganic).

KEY FACT

"**P**oint and **S**hoot": The **P**arasympathetic nervous system mediates erection; the **S**ympathetic nervous system mediates ejaculation.

Diagnosis

Clinical diagnosis.

- Evaluate for neurologic dysfunction (eg, anal tone, lower extremity sensation) and for hypogonadism (eg, small testes, loss of secondary sexual characteristics).
- **Other workup:** Screening for diabetes and cardiovascular disease and measurement of thyroid-stimulating hormone (TSH) and serum testosterone. Elevated prolactin can result in ↓ in androgen activity.

Treatment

- **Best initial treatment:** Patients with psychologic ED may benefit from psychotherapy involving discussion and exercises with the partner.
- Oral sildenafil, vardenafil, and tadalafil are phosphodiesterase-5 (PDE-5) inhibitors that result in prolonged action of cyclic guanosine monophosphate (cGMP)–mediated smooth muscle relaxation and ↑ blood flow in the corpora cavernosa.
- Although sildenafil is useful for patients with ED secondary to cardiovascular disease, use with nitrates is contraindicated.
- Testosterone is a useful therapy for patients with hypogonadism of testicular or pituitary origin; it is discouraged for patients with normal testosterone levels.
- Vacuum pumps, intracavernosal injections of prostaglandins or other vasoactive agents, and surgical implantation of semirigid or inflatable penile prostheses are alternatives for patients for whom PDE-5 therapy fails or is contraindicated.

KEY FACT

Nitrates and PDE-5 inhibitors are a dangerous combination → significant ↓ BP, which can lead to myocardial ischemia.

BENIGN PROSTATIC HYPERPLASIA

Enlargement of the prostate that is a normal part of the aging process and is seen in >80% of males by 80 years of age. Most commonly presents in males >50 years of age. BPH can coexist with prostate cancer, but BPH does not cause prostate cancer. See comparison between BPH and prostate cancer (Table 2.15-9).

TABLE 2.15-9. **Differences Between BPH and Prostate Cancer**

	BPH	PROSTATE CANCER
Risk factor	Age >50 years	Age >40 years, family history
Zone affected	Central	Lateral lobe
Examination	Smooth and symmetrically enlarged	Firms with nodules and asymmetrically enlarged

History/PE

- **Obstructive symptoms:** Hesitancy, weak stream, intermittent stream, incomplete emptying, urinary retention, bladder fullness, acute urinary retention following surgery.
- **Irritative symptoms:** Nocturia, daytime frequency, urge incontinence, opening hematuria.
- On digital rectal exam (DRE), the prostate is uniformly enlarged with a rubbery texture. The physician should suspect cancer if the prostate is hard or has irregular lesions.

Diagnosis

- Obtain a UA and urine culture to rule out infection and hematuria.
- Initial prostate-specific antigen (PSA) testing is controversial, although often ↑ in BPH. Further workup is needed if ↑ PSA correlates with other findings suspicious for prostate cancer.
- Consider creatinine levels to rule out obstructive uropathy and renal insufficiency. Similarly, consider testing electrolytes for any signs of renal tubular dysfunction from an obstruction.

KEY FACT

BPH most commonly occurs in the central (periurethral) zone of the prostate and may not be detected on DRE.

Treatment

- Medical therapy:
  - **Initial treatment:** α-Blockers (eg, tamsulosin, terazosin), which relax smooth muscle in the prostate and bladder neck
  - **Second-line medical treatment:** 5α-Reductase inhibitors (eg, finasteride), which inhibit the production of dihydrotestosterone
- Transurethral resection of the prostate (TURP) or open, laparoscopic, or robotic “simple prostatectomy” is appropriate for patients with moderate to severe symptoms/complications (including renal insufficiency, recurrent UTIs, and bladder stones).
- In case of bladder obstruction, urgent catheterization is necessary while awaiting more definitive management.

UROLOGIC CANCER

PROSTATE CANCER

The most common nonskin cancer in men and the second leading cause of cancer death in males (after lung cancer). Risk factors include advanced age and a ⊕ family history.

KEY FACT

Leading causes of cancer death in men:

1. Lung cancer
2. Prostate cancer
3. Colorectal cancer
4. Pancreatic cancer

History/PE

- Usually asymptomatic but may present with obstructive urinary symptoms. Additional presentations include constitutional symptoms, lymphedema (from metastases obstructing lymphatic drainage), and/or back pain (from bone metastases).
- DRE that may reveal a palpable nodule or an area of induration (see Fig. 2.15-17). Early carcinoma is usually not detectable on exam.

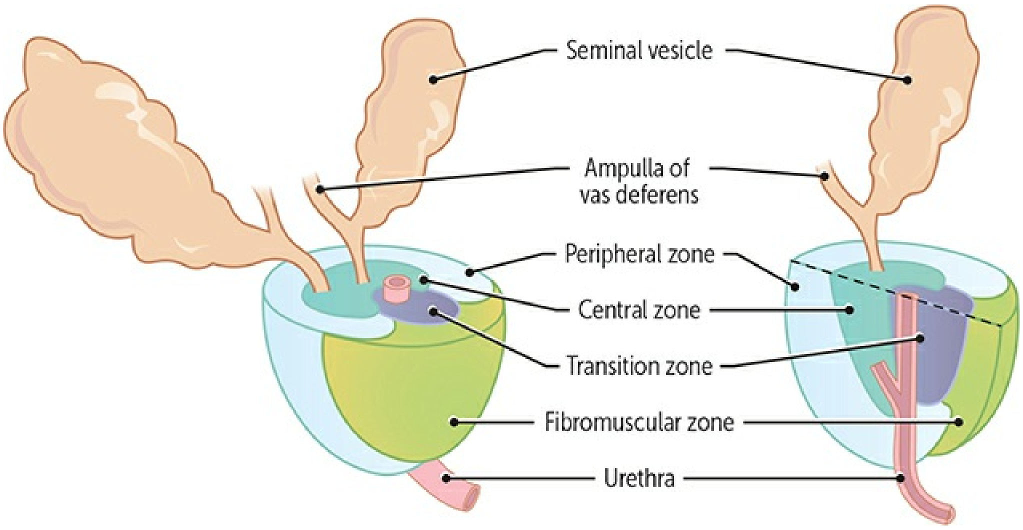


FIGURE 2.15-17. **Structure of the prostate.** (Reproduced with permission from USMLE-Rx.com.)

Diagnosis

- Prostate cancer is suggested by clinical findings and/or a markedly ↑ PSA (>10 ng/mL)
- **Most accurate test:** Transrectal ultrasound-guided biopsy
- The physician should look for metastases with CT of the abdomen/pelvis and a bone scan (metastatic lesions show an osteoblastic or ↑ bone density)

Treatment

- Watchful waiting may be the best approach for older adult patients with low-grade tumors, as many cases of prostate cancer are slow to progress.
- Radical prostatectomy is associated with ↑ risk for incontinence and/or ED.
- Radiation therapy (eg, brachytherapy or external beam) is associated with ↑ risk for

radiation proctitis and GI symptoms. Also associated with increased risk for ED posttreatment.

- PSA, although controversial as a screening test, is used to follow a patient posttreatment to evaluate for disease recurrence.
- The physician can treat metastatic disease with androgen ablation (eg, gonadotropin-releasing hormone agonists, orchiectomy, bicalutamide) and chemotherapy.
- Radiation therapy is useful to manage bone pain from metastases after androgen ablation.

KEY FACT

An ↑ PSA can be caused by BPH, prostatitis, prostatic trauma, or carcinoma.

MNEMONIC

Differential for hematuria—

I PEE RBCS

Infection (UTI)
Polycystic kidney disease
Exercise
External trauma
Renal glomerular disease
Benign prostatic hyperplasia
Cancer, **C**ongenital anomalies/obstruction, **C**ysts, Hyper**C**alciuria, **C**rystals
Stones, **S**ickle cell

Prevention

Screening guidelines remain controversial. Males should discuss the pros and cons of annual DRE and/or PSA testing starting at 50 years of age. Screening should begin earlier in Black males and in those with a first-degree relative with prostate cancer.

BLADDER CANCER

The second most common urologic cancer and the most frequent malignant tumor of the urinary tract; usually a transitional cell carcinoma—now called urothelial carcinoma (see Fig. 2.15-18). Most prevalent in males during the sixth and seventh decades. Risk factors include smoking, diets rich in meat and fat, schistosomiasis (squamous cell carcinoma), past treatment with cyclophosphamide, and occupational exposure to aniline dye.

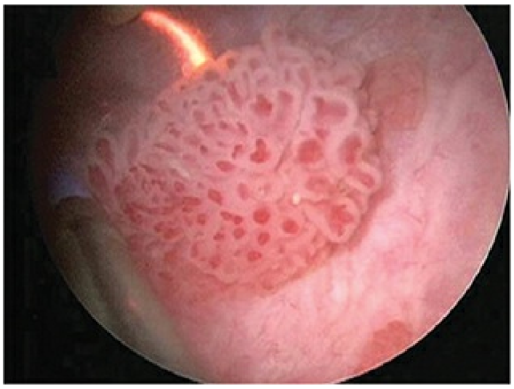


FIGURE 2.15-18. **Transitional cell carcinoma of the bladder.** Cystoscopic image of bladder wall mass. (Modified with permission from Geavlete B, Stanescu F, Moldoveanu C, et al. NBI cystoscopy and bipolar electrosurgery in NMIBC management—an overview of daily practice. *J Med Life.* 2013;6[2]:140–145.

History/PE

- Gross, painless hematuria is the most common presenting symptom. Terminal hematuria (end of voiding) suggests bleeding from the bladder.
- Other urinary symptoms, such as frequency, urgency, and dysuria, can also be seen, but most patients are asymptomatic in the early stages of the disease.

Diagnosis

- Screening is not recommended.
- UA often shows hematuria (macroscopic or microscopic).
- Cystoscopy with biopsy is diagnostic and is recommended in the evaluation of adults >35 years of age with unexplained hematuria.
- Urine cytology may show dysplastic cells.
- MRI, CT, and bone scan are important tools with which to define muscle invasion and metastases.

Treatment

Treatment depends on the extent of spread beyond the bladder mucosa.

- **Carcinoma in situ:** Intravesicular chemotherapy or transurethral resection
- **Superficial cancers:** Complete transurethral resection or intravesicular chemotherapy with mitomycin-C or Bacille Calmette-Guérin ([BCG], the TB vaccine)
- **Large, high-grade recurrent lesions:** Intravesicular chemotherapy
- **Invasive cancers without metastases:** Radical cystectomy or radiation therapy for patients who are deemed poor candidates for radical cystectomy and for those with unresectable local disease. Neoadjuvant systemic therapy and radiosensitization is often considered.
- **Invasive cancers with distant metastases:** Chemotherapy, immunotherapy, and novel targeted agents are considered.

KEY FACT

A key step for diagnosis in an adult patient with unexplained hematuria is cystoscopy to evaluate for bladder cancer.

RENAL CELL CARCINOMA

An adenocarcinoma from tubular epithelial cells (~80%–90% of all malignant tumors of the kidney). Tumors can spread along the renal vein to the inferior vena cava (IVC) and metastasize to other sites, eg, lung, bone, brain, and liver. Risk factors include male sex, smoking, obesity, acquired cystic kidney disease in ESRD, and certain genetic conditions, such as von Hippel–Lindau disease.

History/PE

Presenting signs include gross hematuria, flank pain, scrotal varicoceles, and a palpable flank mass. Metastatic disease can present with weight loss and malaise. Paraneoplastic symptoms include anemia, erythropoiesis, thrombocytosis, fever, cachexia, hypercalcemia, and polymyalgia rheumatica.

KEY FACT

The classic triad of renal cell carcinoma consists of hematuria, flank pain, and a palpable flank mass, but only 5% to 10% present with all three components of the triad.

KEY FACT

In a middle-aged individual with a history of smoking and a left-sided varicocele, consider renal cell carcinoma!

Diagnosis

Best initial test: Diagnosed via CT (see Fig. 2.15-19) to characterize the renal mass and stage for lymph nodes/metastases. Ultrasonography rarely used. Diagnosis is then confirmed by histology on nephrectomy specimen.

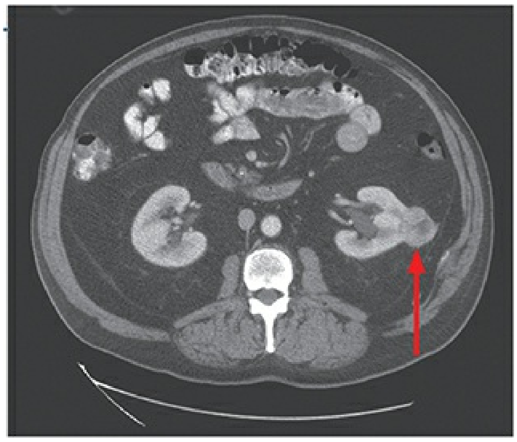


FIGURE 2.15-19. **Renal cell carcinoma.** A contrast-enhanced CT through the abdomen demonstrates an enhancing exophytic mass *(arrow)* in the left kidney that proved on pathology to be renal cell carcinoma. (Reproduced with permission from Doherty GM. *Current Diagnosis & Treatment: Surgery*, 13th ed. New York, NY: McGraw-Hill; 2010.)

Treatment

- Surgical resection or thermal ablation may be curative in localized disease.

Metastasectomy may improve survival in metastatic disease.

- Response rates from radiation or chemotherapy are only 15% to 30%. Newer tyrosine kinase inhibitors (axitinib, lenvatnib, cabozatonib), which ↓ tumor angiogenesis and cell proliferation, have shown promising results.

TESTICULAR CANCER

A heterogeneous group of neoplasms. About 95% of testicular tumors derive from germ cells, and virtually all are malignant. Risk factors include cryptorchidism, Klinefelter syndrome, and ⊕ family history. Testicular cancer is the most common malignancy in males 15 to 34 years of age.

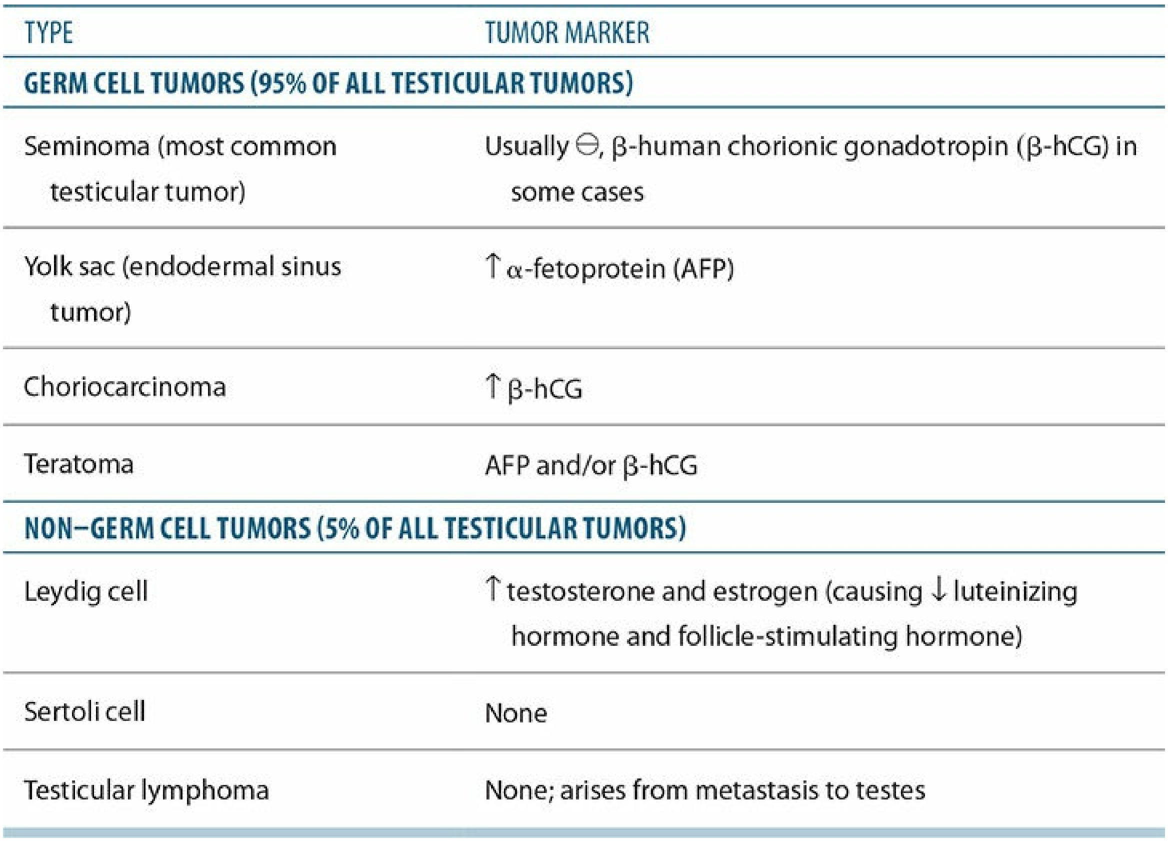
History/PE

- Patients most often present with painless enlargement of the testes, a firm ovoid mass with possible nodules, dull abdominal pain, and metastatic symptoms (lower back pain, dyspnea, cough and retroperitoneal lymphadenopathy).
- Most testicular cancers occur between 15 and 30 years of age, but seminomas have a peak incidence between 40 and 50 years of age.

Diagnosis

- Testicular ultrasonography
- CXR and CT of the abdomen/pelvis to evaluate for metastasis
- Tumor markers are useful for diagnosis and in monitoring treatment response (see Table 2.15-10)

TABLE 2.15-10. Tumor Markers in Testicular Cancer



TYPE	TUMOR MARKER
GERM CELL TUMORS (95% OF ALL TESTICULAR TUMORS)	
Seminoma (most common testicular tumor)	Usually ⊖, β-human chorionic gonadotropin (β-hCG) in some cases
Yolk sac (endodermal sinus tumor)	↑ α-fetoprotein (AFP)
Choriocarcinoma	↑ β-hCG
Teratoma	AFP and/or β-hCG
NON–GERM CELL TUMORS (5% OF ALL TESTICULAR TUMORS)	
Leydig cell	↑ testosterone and estrogen (causing ↓ luteinizing hormone and follicle-stimulating hormone)
Sertoli cell	None
Testicular lymphoma	None; arises from metastasis to testes

- Biopsy is contraindicated due to the risk of spillage of cancer cells

KEY FACT

β-hCG in males = choriocarcinoma

Treatment

- Radical orchiectomy and classification as seminoma or nonseminomatous germ cell tumor (NSGCT)
  - Seminoma: Chemotherapy or radiation therapy for low-stage disease
  - NSGCT: Retroperitoneal lymph node dissection for low-stage disease
- Platinum-based chemotherapy used for advanced disease of either type

GENITOURINARY INFECTIONS

URINARY TRACT INFECTIONS

Table 2.15-11 provides an overview/review of the types of UTIs, criteria, and treatment. The rest of this section will further explore acute (uncomplicated) simple cystitis, as well as pyelonephritis + prostatitis (both types of complicated UTIs).

TABLE 2.15-11. Types of UTIs, Criteria, and Treatment

TYPE	CRITERIA	TREATMENT
Uncomplicated UTI	Lower UTI is acute, simple cystitis (classic symptoms: dysuria, frequency, urgency, suprapubic pain) in an otherwise healthy, nonpregnant female who has not failed antibiotic therapy Infection is confined to bladder (cystitis) Patient has no systemic symptoms of an acute, complicated UTI	Trimethoprim-sulfamethoxazole (TMP-SMX) for 3 days Nitrofurantoin (5–7 days), but only effective for cystitis; if suspect a possibility for pyelonephritis or complicated UTI, should not use nitrofurantoin Culturing is ONLY recommended if treatment fails
Complicated UTI	Simply summarized: A complicated UTI is one that does not meet criteria for uncomplicated This may be a presentation similar to that of an uncomplicated UTI, but in a population at higher risk for complexity, such as a pregnant woman, a patient with comorbidities (such as diabetes), infants and toddlers, and male sex; it would also include those with immunocompromise or stents or urinary catheters, as well as those with recurrent or refractory UTIs A complicated UTI would also be any patient with systemic symptoms of UTI that might suggest pyelonephritis, such as fever, chills, vomiting, abdominal or flank pain, or costovertebral angle tenderness on exam	For otherwise healthy patients who are hemodynamically stable and can tolerate oral antibiotics, treatment is given as outpatient, often with floroquinolones, third-/fourth-generation cephalosporins, or TMP-SMX For patients who are hemodynamically unstable, who have sepsis, or who cannot tolerate oral antibiotics, IV third-/fourth-generation cephalosporins are typically given, or floroquinolones
Pregnancy UTI	In pregnant patients, urinalysis is routinely performed to screen for asymptomatic bacteriuria Pregnant patients may also present with acute cystitis (as noted earlier) and would be considered a complicated UTI and treated as such Pregnant patients are at increased risk for pyelonephritis and urosepsis	Asymptomatic bacteria does not normally require treatment; however, due to increased risk for complications, pregnant women with asymptomatic bacteria are treated with either nitrofurantoin or amoxicillin with follow-up culture to confirm resolution Treatment of cystitis and pyelonephritis would be as for treatment of complicated UTI
Prophylaxis of UTIs	Suitable for a patient with recurrent UTIs (two or more infections in 6 months or three or more infections in 1 year); behavioral modifications are first line and include ↑ fluid intake (promoting urinary flow so that microbes cannot as easily ascend the urinary tract), postcoital voiding/stoppage of spermicide use, and vaginal estrogen in postmenopausal females	If behavioral modifications are ineffective: Antibiotic prophylaxis (TMP-SMX or nitrofurantoin) after intercourse, first sign(s) of symptoms; the physician can prescribe antibiotics at a low dose for 3–6 months or continuously
Bladder pain syndrome + UTI mimics	Interstitial cystitis = bladder pain syndrome → chronic suprapubic pain/discomfort, dysuria, frequency, dyspareunia, pelvic pain, relief after voiding that lasts >6 weeks without an underlying medical cause; classically in women with psychiatric disease (analogous to fibromyalgia, IBS); notably, painful bladder syndrome is a UTI mimic; other UTI mimics include hemorrhagic cystitis (after cyclophosphamide) and bladder irritation from radiation therapy to pelvis	**First-line treatment: Avoid dietary triggers** Amitriptyline, pain management (phenazopyridine or methenamine), bladder hydrodistention

Microbiology

- UTIs most commonly result from ascending infection from the urethra → prostate (prostatitis) → bladder (cystitis) → kidney (pyelonephritis) → systemic (urosepsis). Due to this “ascension,” these infections share common microbiologic profiles, as captured in Table 2.15-12.

TABLE 2.15-12. **Microbiology of UTIs**

SPECIES	FEATURES	COMMENTS
Escherichia coli	Leading cause of UTIs	Diagnostic markers: ⊕ Leukocyte esterase = evidence of WBC activity ⊕ Nitrite test = reduction of urinary nitrates by gram ⊖ bacterial species (eg, *E coli*)
Staphylococcus saprophyticus	Second leading cause of UTIs, particularly in young, sexually active females	
Klebsiella pneumoniae	Third leading cause of UTIs	
Serratia marcescens	Some strains revealed by red pigment Often health care associated and drug resistant	
Enterococcus	Often health care associated and drug resistant	
Proteus mirabilis	Produces urease Associated with struvite stones	
Pseudomonas aeruginosa	Usually health care associated and drug resistant	

- Cystitis presents with dysuria, frequency, urgency, suprapubic pain, and WBCs (but not WBC casts) in urine. Primarily caused by ascension of microbes from urethra to bladder. Ascension to kidney results in pyelonephritis, which presents with fever, chills, flank pain, costovertebral angle (CVA) tenderness, hematuria, and WBC casts.
- Ten times more common in females (shorter urethras colonized by fecal microbiota).
- **Risk factors:** Obstruction (eg, kidney stones, enlarged prostate), kidney surgery, catheterization, congenital genitourinary (GU) malformation (eg, vesicoureteral reflux), diabetes, pregnancy.

MNEMONIC

Common UTI bugs—

SEEKS PP

_S_*erratia*
_E_*scherichia coli*
_E_*nterobacter*
_K_*lebsiella pneumoniae*
_S_*taphylococcus saprophyticus*
_P_*seudomonas*
_P_*roteus mirabilis*

UNCOMPLICATED UTI/LOWER UTI/ACUTE SIMPLE CYSTITIS

History/PE

Classic tetrad of frequent SUD: frequency (voiding a lot) + Suprapubic pain + Urgency (feeling need to void) + Dysuria (burning, painful voiding). Fever + systemic signs are characteristically absent in simple cystitis → plasma WBC count being normal.

Diagnosis

Clinical diagnosis is sufficient in symptomatic (frequent SUD), uncomplicated lower UTIs in nonpregnant women → begin treatment. Other patients → best initial test = UA.

Treatment

- **General guidelines:** Treated on clinical diagnosis alone
- **First-line antibiotics:** TMP-SMX (3 days), nitrofurantoin (5–7 days)
- **Pain:** Pentosan (relieves cystitis pain) or phenazopyridine (relieves urinary tract pain)

PYELONEPHRITIS/UPPER UTI/ONE FORM OF COMPLICATED UTI

History/PE

Infection ascends from urethra → bladder (cystitis symptoms of frequency + suprapubic pain + urgency + dysuria) → kidney (pyelonephritis symptoms of CVA tenderness + flank pain) → systemic infection (symptoms of fever + chills + tachycardia) → eventually to urosepsis (10%–25% of cases).

Diagnosis

Clinical diagnosis supported by cultures (see Fig. 2.15-20).

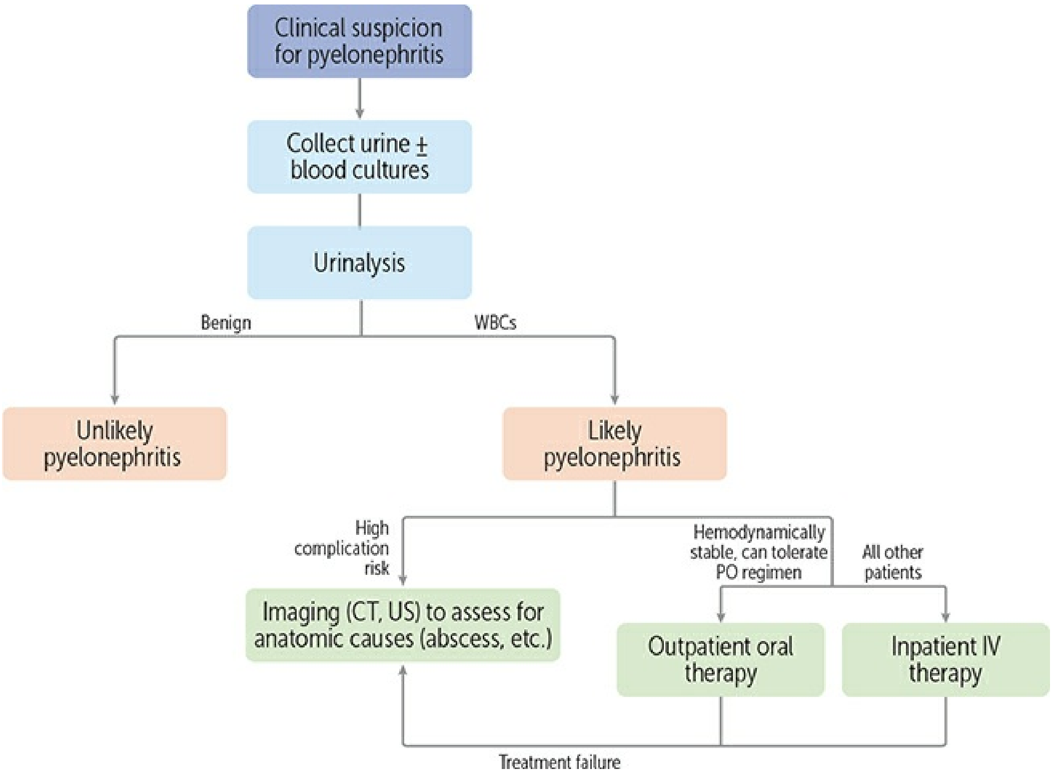

Clinical suspicion for pyelonephritis
Collect urine ± blood cultures
Urinalysis
Benign
WBCs
Unlikely pyelonephritis
Likely pyelonephritis
High complication risk
Hemodynamically stable, can tolerate PO regimen
All other patients
Imaging (CT, US) to assess for anatomic causes (abscess, etc.)
Outpatient oral therapy
Inpatient IV therapy
Treatment failure

FIGURE 2.15-20. **Pyelonephritis algorithm.** (Reproduced with permission from USMLE-Rx.com.)

- **Cultures:** All patients should have urine cultures collected prior to empiric antibiotic therapy. Therapy is tailored based on cultures.
- **UA:** Similar findings to uncomplicated simple cystitis (see earlier section) + WBC casts (infection in kidney → casts form as WBCs infiltrate tubules).
- **Imaging (CT, ultrasound):** Reserved for patients at high risk for complications (a complicated UTI = complicated pyelonephritis) and treatment failure. Imaging examines anatomic causes + abscess formation + emphysematous pyelonephritis.

Complications

- **Abscesses** can form in the renal parenchyma and/or in the perirenal fat (perinephric abscess). Patients who have persistent fever + abdominal pain despite adequate antibiotic treatment → CT/ultrasound imaging → diagnose abscess → drainage (all perinephric, >5 cm renal) + continued antibiotics.
- **Emphysematous pyelonephritis** → caused by gas-producing bacteria (see Fig. 2.15-21A), classically in patients with diabetes or immunocompromise.

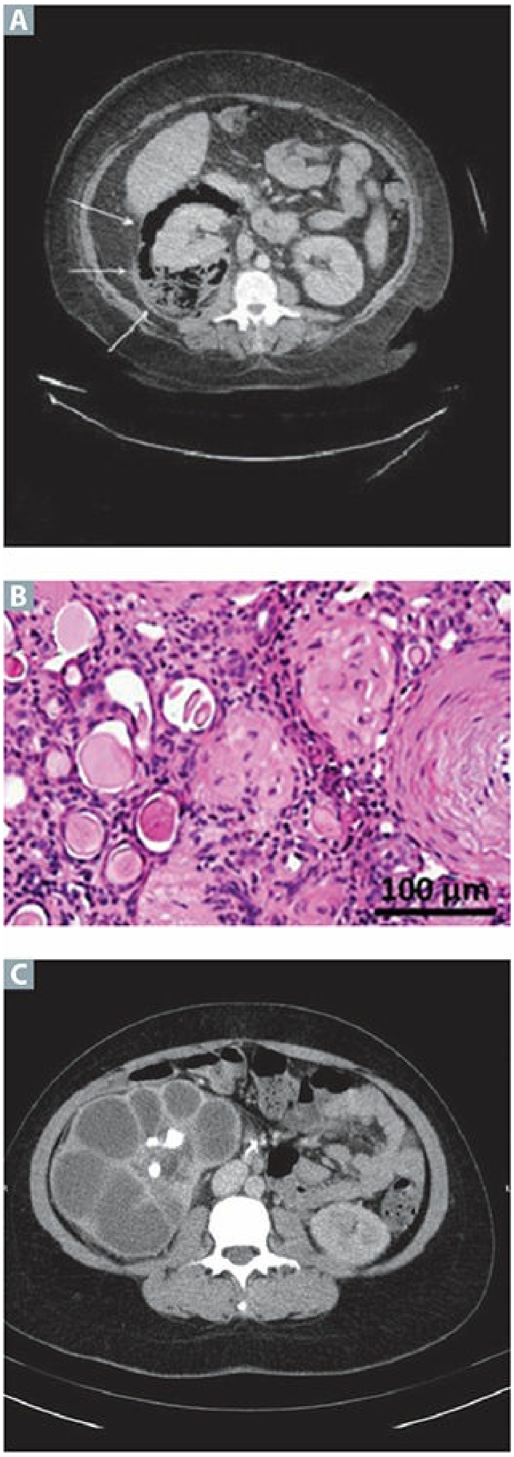


FIGURE 2.15-21. **Pyelonephritis findings. (A)** Emphysematous pyelonephritis. (arrows indicate air pockets from gas-producing bacteria) **(B)** Thyroidization of the kidney in chronic pyelonephritis. **(C)** Bear paw sign in xanthogranulomatous pyelonephritis. (Image A reproduced with permission from Ünlüer EE, Karagöz A. Computed tomography in emphysematous pyelonephritis. *Pan Afr Med J.* 2015;22:186. Published 2015 Oct 23. doi:10.11604/pamj.2015.22.186.7902. Image B reproduced with permission from Bilgrami SM, Qureshi SA, Pervez S, Abbas F. Promoter hypermethylation of tumor suppressor genes correlates with tumor grade and invasiveness in patients with urothelial bladder cancer. *Springerplus.* 2014 Apr 5;3:178. doi: 10.1186/2193-1801-3-178. Image C adapted with permission from Ferreira L, Oliveira C, Cruz C, Pacheco A. Xanthogranulomatous pyelonephritis associated with hepatic dysfunction in pregnancy. *Case Rep Obstet Gynecol.* 2015;2015:936262. doi:10.1155/2015/936262.)

- **Chronic pyelonephritis** is caused by recurrent pyelonephritis (classically in children with with vesicoureteral reflux (VUR) + obstruction in adults (recurrent kidney stones, BPH, cervical carcinoma) → blunted calyces + corticomedullary scarring of the kidneys (seen on imaging, upper/lower pole scarring is characteristic of VUR). Pathologic examination → interstitial fibrosis + thyroidization of kidney (atrophic tubules filled with eosinophilic proteaceous materials, see Fig. 2.15-21B).

- Xanthogranulomatous pyelonephritis is a severe form of chronic pyelonephritis caused by infected kidney stone obstruction → granulomatous inflammation → multiple, dark round areas on CT (Bear Paw sign; see Fig. 2.15-21C).

Treatment

- Hemodynamically stable, can tolerate oral intake:
  - Outpatient care → fluroquinolones or third-/fourth-generation cephalosporin or TMP-SMX for 7 to 14 days
  - Overall, culture results, collected in ALL patients with pyelonephritis → treatment selection
- All other patients (hemodynamically unstable, critically ill, urinary obstruction/prosthetics):
  - Inpatient care → parenteral antibiotics such as ceftriaxone, ampicillin/sulbactam, piperacillin/tazobactam, and fluroquinolones—guided by local sensitivity patterns and culture results)

KEY FACT

Nitrofurantoin and fosfomycin ONLY achieve therapeutic concentrations in the bladder + urine, and they do **not** penetrate renal parenchyma, so they should only be used to treat cystitis, **not** pyelonephritis.

PROSTATITIS: ONE FORM OF COMPLICATED UTI

Infection ascends from the urethra + reflux of infected urine → prostate (acute/chronic prostatitis). In both acute and chronic prostatitis, common UTI pathogens predominant (especially gram-negative *E coli*, which is still the most common). With acute bacterial prostatitis more common in younger males (age <40 years), high-risk sexual behaviors increase the risk of *N gonorrhoeae* and *Chlamydia trachomatis* infections. Chronic bacterial prostatitis is more common, occurs in older males (age 40–70 years), and may result from acute prostatitis.

History/PE

- Acute prostatitis classically presents with an ill appearance, including systemic symptoms (fever + chills) + prostatitis symptoms (perineal pain + low back pain + pain with defecation) + irritative urinary symptoms (dysuria—burning pain when voiding) + frequency + urgency → urinary retention. DRE reveals an exquisitely tender + boggy prostrate. Prostatic massage must be avoided in acute bacterial prostatitis, as it can cause bacteremia. DRE can even be skipped, as the diagnosis can be made on clinical presentation alone.
- Chronic prostatitis may be less symptomatic + patients do not appear ill + fever is usually absent. Patients may report prostatitis symptoms (dull, poorly localizable pain in the low back + perineal + scrotal + suprapubic regions) + recurrent urinary symptoms (dysuria + frequency + urgency + obstructive symptoms + ED ± bloody semen) with repeated

isolation of the same organism from urine cultures. DRE reveals an enlarged, nontender prostrate.

Diagnosis

- Acute prostatitis is confirmed by UA (sheets of WBCs + bacteriuria) + urine culture (*E coli* is most commonly cultured). Obtain blood cultures in very ill-appearing or hemodynamically unstable patients.
- Chronic prostatitis is suggested by the presence of WBCs in expressed prostatic secretions. Urine culture is ⊕ in chronic bacterial prostatitis and ⊖ in chronic nonbacterial prostatitis. The four-glass test can be used to determine the location of infection as secretions are cultured: first glass (initial urine = urethra sample), second glass (midstream urine = bladder sample), third glass (prostatic massage = prostate sample), fourth glass (after prostatic massage = another prostatic sample). Alternatively, the two-glass test can be used, which is simply glasses 3 and 4 in the previous test.

Treatment

- Acute prostatitis if severe, hospitalization + IV antibiotics (fluoroquinolone ± third-/fourth-generation cephalosporin). If mild, outpatient TMP-SMX or fluroquinolone (ciprofloxacin or levofloxacin) for 4 to 6 weeks to achieve therapeutic levels in prostate. Men who engage in high-risk sexual activity should be considered for *N gonorrhoeae* and *C trachomatis* coverage (ceftriaxone + azithromycin or doxycycline).
- Chronic prostatitis → TMP-SMX or fluroquinolone (ciprofloxacin or levofloxacin) for 6 to 8 weeks → achieve therapeutic levels in prostate. Treatment is difficult; UTI recurrences are common.

KEY FACT

Asymptomatic bacteriuria is ONLY treated in pregnancy and before urologic surgery. Pyelonephritis develops in 20% to 30% of pregnant patients with untreated asymptomatic bacteriuria.

KEY FACT

Prostatic massage is avoided in patients with acute bacterial prostatitis, as it can cause bacteremia. Digital rectal exam can even be skipped in the setting of a convincing clinical presentation.

SEXUALLY TRANSMITTED DISEASES

CHLAMYDIA

The most common bacterial sexually transmitted disease (STD) in the United States. Caused by *C trachomatis,* which can infect the genital tract, urethra, anus, and eye. Risk factors include unprotected sexual intercourse and new or multiple partners. Often coexists with or mimics *N gonorrhoeae* infection (known as nongonococcal urethritis when gonorrhea is absent). Lymphogranuloma venereum (LGV) serovars of *C trachomatis* cause LGV, an emerging cause of proctocolitis.

History/PE

- Infection is often asymptomatic in males and may present with urethritis, mucopurulent cervicitis, or pelvic inflammatory disease (PID) in women.
- Exam may reveal cervical/adnexal tenderness in women or penile discharge and testicular tenderness in men.
- The differential diagnosis includes gonorrhea, endometriosis, PID, orchitis, vaginitis, and UTI.
- LGV presents in its primary form as a painless, transient papule or shallow ulcer. In its secondary form, it presents as painful swelling of the inguinal nodes, and in its tertiary form, it can present as an "anogenital syndrome" (anal pruritus with discharge, rectal strictures, rectovaginal fistula, and elephantiasis).

KEY FACT

Chlamydia species cause arthritis, neonatal conjunctivitis, pneumonia, nongonococcal urethritis/PID, and LGV.

Diagnosis

- Diagnosis is usually clinical; culture is the **gold standard**.
- Urine tests (nucleic acid amplification test) are a rapid means of detection, whereas DNA probes and immunofluorescence (for gonorrhea/chlamydia) take 48 to 72 hours.
- A Gram stain of urethral or genital discharge may show polymorphonuclear (PMN) leukocytes but no bacteria, as *Chlamydia* is an intracellular organism.

Treatment

- Doxycycline for 7 days or azithromycin once. Pregnant patients should take azithromycin or amoxicillin.
- Treatment of sexual partners. The physician should maintain a low threshold to also treat for concurrent *N gonorrhoeae*, as they often coexist. LGV serovars require prolonged therapy for 21 days.

Complications

- Chronic infection and pelvic pain, Reiter syndrome (urethritis, conjunctivitis, arthritis), Fitz-Hugh–Curtis syndrome (perihepatic inflammation and fibrosis). See Figures 2.15-22 and 2.15-23.

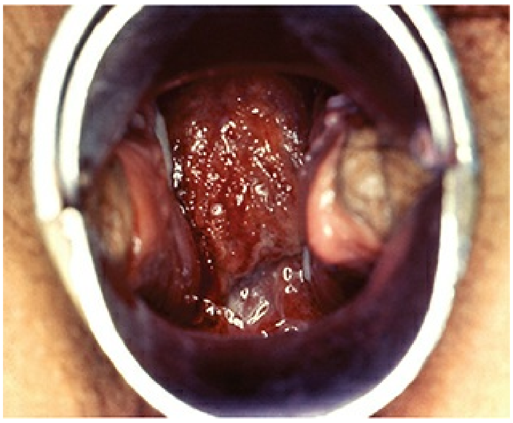


FIGURE 2.15-22. **Purulent cervical discharge in pelvic inflammatory disease.** (Reproduced courtesy of US Department of Health and Human Services and Dr. Lourdes Fraw and Jim Pledger.)

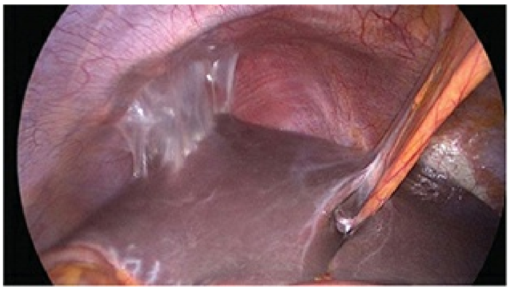


FIGURE 2.15-23. **Adhesions in Fitz-Hugh–Curtis syndrome in pelvic inflammatory disease.** Note the adhesions extending from the peritoneum to the surface of the liver. (Reproduced with permission from Kardakis S, Barranca A, Vitelli A, et al. Isolated fallopian tube torsion. *Case Rep Obstet Gynecol.* 2013;2013:479698. doi: 10.1155/2013/479698.)

- Ectopic pregnancy/infertility can result from PID (in women) and epididymitis (in men).

GONORRHEA

An infection caused by a gram ⊖ intracellular diplococcus that can infect almost any site in the female reproductive tract. Infection in males tends to be limited to the urethra.

History/PE

- Presents with a greenish-yellow discharge, pelvic or adnexal pain, and swollen Bartholin glands. Men experience a purulent urethral discharge, dysuria, and erythema of the urethral meatus.
- The differential diagnosis includes chlamydia, endometriosis, pharyngitis, PID, vaginitis, UTI, salpingitis, and tubo-ovarian abscess.

Diagnosis

- **Gold standard:** Gram stain and culture for any site (pharynx, cervix, urethra, or anus). Nucleic acid amplification tests can be sent on penile/vaginal tissue or from urine.
- Disseminated disease may present with monoarticular septic arthritis, rash, and/or tenosynovitis. See Figures 2.15-24 and 2.15-25.

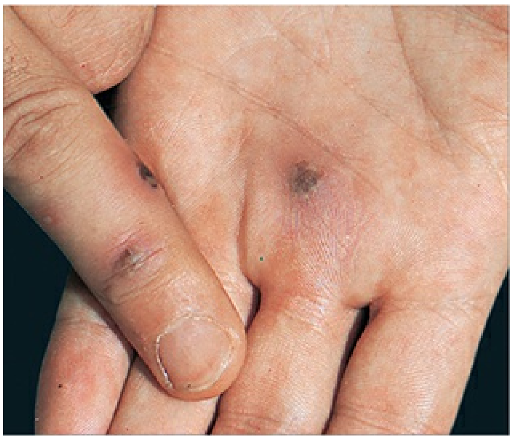


FIGURE 2.15-24. **Disseminated gonococcal infection.** Hemorrhagic, painful pustules are seen on erythematous bases. (Reproduced with permission from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine,* 7th ed. New York, NY: McGraw-Hill; 2008.)

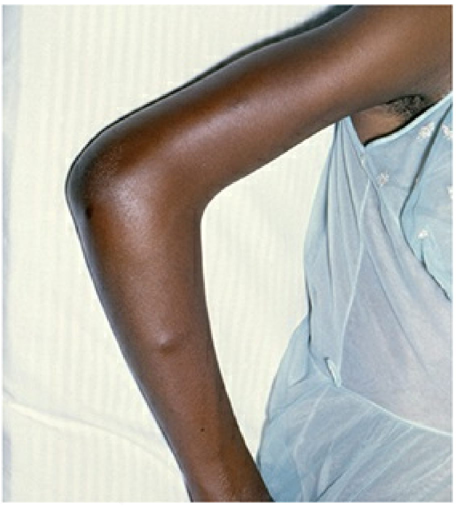


FIGURE 2.15-25. ***Neisseria gonorrhoeae* joint infection.** (Reproduced courtesy of US Department of Health and Human Services and Emory.)

Treatment

Intramuscular (IM) ceftriaxone and oral (PO) azithromycin (regardless of whether chlamydia is present). Condoms are effective prophylaxis. The sexual partner or partners should be treated if possible. Fluoroquinolones should not be used because of emerging resistance.

Disseminated disease requires IV ceftriaxone for at least 24 hours.

KEY FACT

Treat gonorrhea with two agents because of the high prevalence of resistance.

Complications

Persistent infection with pain; infertility; tubo-ovarian abscess with rupture; disseminated gonococcal infection (characterized by migratory polyarthralgia, tenosynovitis, and pustular skin lesions) (see Fig. 2.15-25).

SYPHILIS

Caused by *Treponema pallidum*, a spirochete. AIDS can accelerate the course of disease progression.

History/PE

- **Primary (10–90 days after infection):** Presents with a painless ulcer (chancre; see Fig. 2.15-26A and B) and local lymphadenopathy.

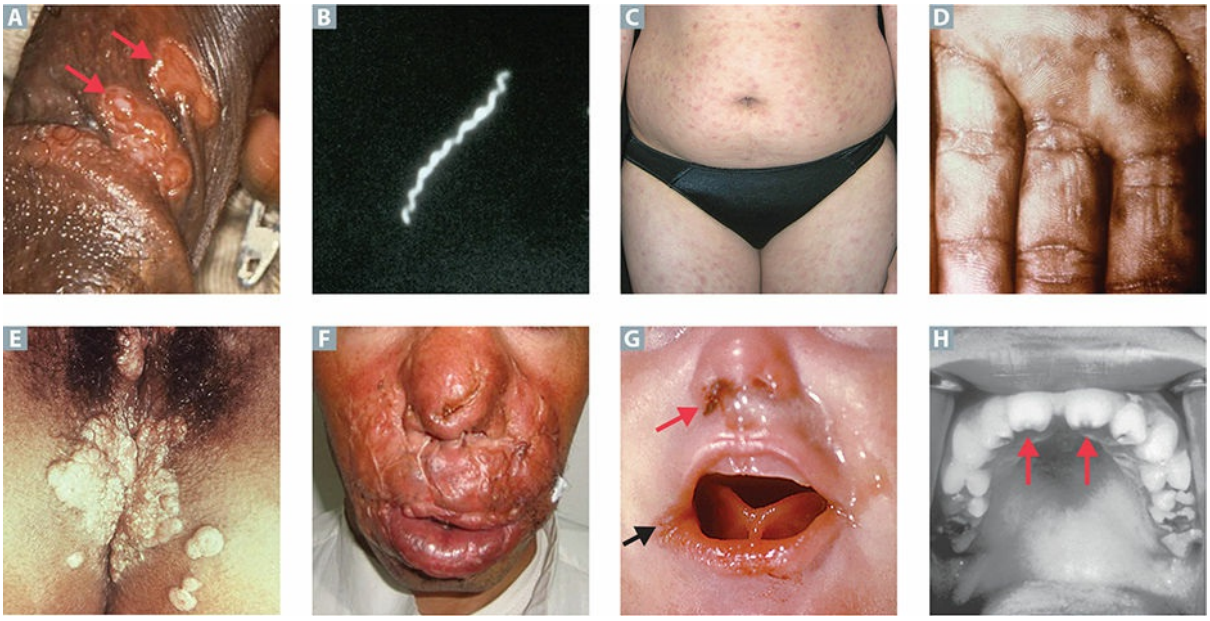


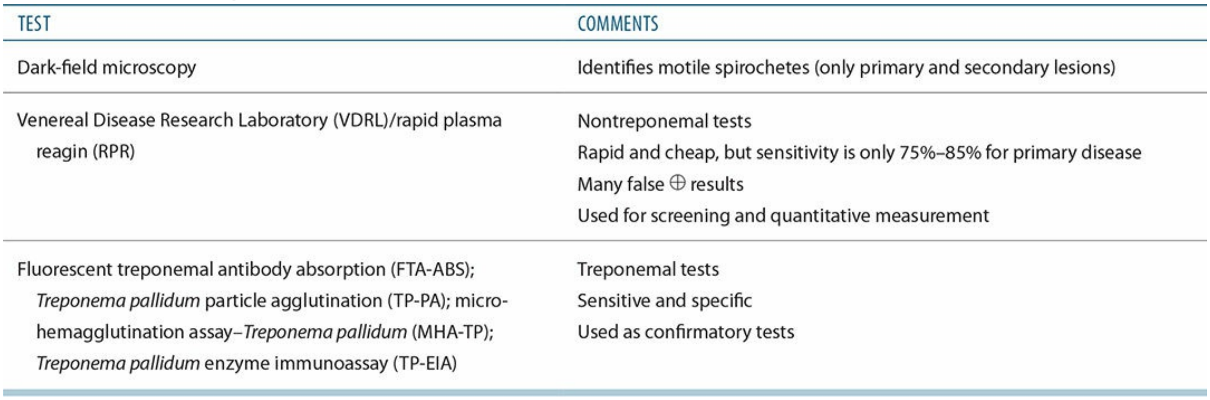
FIGURE 2.15-26. **Syphilis. (A)** Localized disease presenting with painless chancre. **(B)** Dark-field microscopy visualizing treponemes in fluid from chancre in primary syphilis. **(C)** Maculopapular rash (**[D]** including palms and soles) and **(E)** condylomata lata in secondary syphilis. **(F)** Gummas (chronic granulomas) in tertiary syphilis. **(G)** Rhagades (linear scars at angle of mouth), snuffles (nasal discharge), saddle nose, and **(H)** notched (Hutchinson) teeth in congenital syphilis. (Image A reproduced courtesy of the US Department of Health and Human Services and M. Rein. Image B reproduced courtesy of the US Department of Health and Human Services and Renelle Woodall. Image C reproduced with permission from Dr. Richard Usatine. Image D reproduced courtesy of the US Department of Health and Human Services and Robert Sumpter. Images E and H reproduced courtesy of the US Department of Health and Human Services and Susan Lindsley. Image F modified with permission from Chakir K, Benchikhi H. Centro-facial granuloma revealing a tertiary syphilis. *Pan Afr Med J*. 2013;15:82. Image G reproduced courtesy of the US Department of Health and Human Services and Dr. Norman Cole.)

- **Secondary (4–8 weeks after chancre):** Presents with low-grade fever, headache, malaise, and generalized lymphadenopathy with a diffuse, symmetric, asymptomatic (nonpruritic) maculopapular rash on the soles and palms (see Figs. 2.15-26C and D). Highly infective secondary eruptions include mucus patches called condylomata lata (see Fig. 2.15-26E) and alopecia. Meningitis, hepatitis, nephropathy, and eye involvement may also be seen.
  - **Early latent (period from resolution of primary or secondary syphilis to the end of the first year of infection):** No symptoms; ⊕ serology.
  - **Late latent (period of asymptomatic infection beyond the first year):** No symptoms; ⊕ or ⊖ serology. One third of cases progress to tertiary syphilis.
- **Tertiary (late manifestations appearing 1–20 years after initial infection):** Presents with destructive, granulomatous gummas (see Fig. 2.15-26F). Neurosyphilis includes tabes dorsalis (posterior column degeneration), meningitis, and Argyll Robertson pupil (constricts with accommodation but not reactive to light). Cardiovascular findings include dilated aortic root, aortitis, aortic root aneurysms, and aortic regurgitation.

Diagnosis

Table 2.15-13 summarizes relevant diagnostic tests.

TABLE 2.15-13. Diagnostic Tests for Syphilis



TEST	COMMENTS
Dark-field microscopy	Identifies motile spirochetes (only primary and secondary lesions)
Venereal Disease Research Laboratory (VDRL)/rapid plasma reagin (RPR)	Nontreponemal tests Rapid and cheap, but sensitivity is only 75%–85% for primary disease Many false ⊕ results Used for screening and quantitative measurement
Fluorescent treponemal antibody absorption (FTA-ABS); *Treponema pallidum* particle agglutination (TP-PA); microhemagglutination assay–*Treponema pallidum* (MHA-TP); *Treponema pallidum* enzyme immunoassay (TP-EIA)	Treponemal tests Sensitive and specific Used as confirmatory tests

Venereal Disease Research Laboratory (VDRL) test: False ⊕ results are seen with viruses (mononucleosis, herpes simplex virus [HSV], HIV, hepatitis), IV drug use, rheumatic fever, rheumatoid arthritis, SLE, and leprosy.

Neurosyphilis should be suspected and ruled out in patients with AIDS, neurologic symptoms, and a ⊕ rapid plasma reagin (RPR) test.

KEY FACT

Syphilis is the “great imitator” because its dermatologic findings resemble those of many other diseases.

KEY FACT

Treatment of syphilis can result in an acute flulike illness (headache, fever, chills, myalgias) known as the Jarisch-Herxheimer reaction, which results from the release of endotoxins by the killed organisms.

Treatment

See the syphilis management algorithm in Figure 2.15-27.

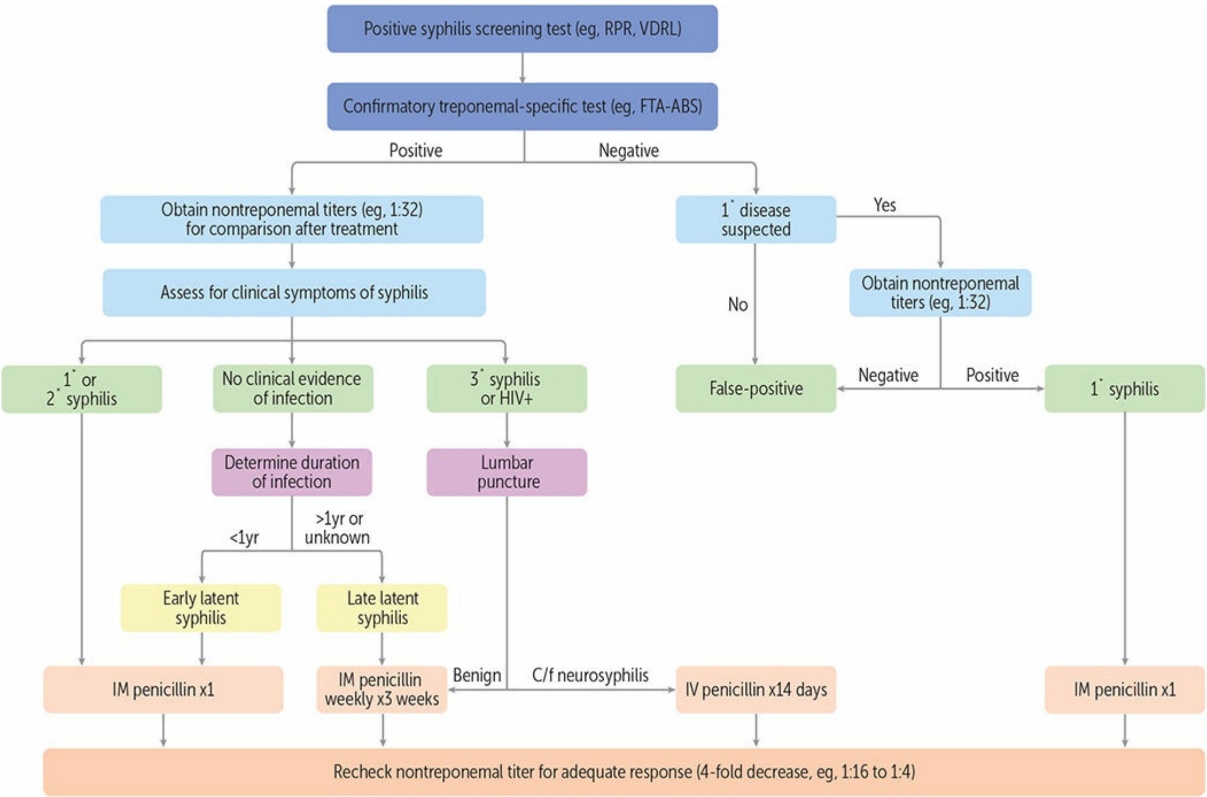

Positive syphilis screening test (eg, RPR, VDRL)
Confirmatory treponemal-specific test (eg, FTA-ABS)
Positive
Negative
Obtain nontreponemal titers (eg, 1:32) for comparison after treatment
Assess for clinical symptoms of syphilis
1° or 2° syphilis
No clinical evidence of infection
3° syphilis or HIV+
Determine duration of infection
Lumbar puncture
<1yr
>1yr or unknown
Early latent syphilis
Late latent syphilis
IM penicillin x1
IM penicillin weekly x3 weeks
Benign
C/f neurosyphilis
IV penicillin x14 days
1° disease suspected
Yes
No
Obtain nontreponemal titers (eg, 1:32)
False-positive
Negative
Positive
1° syphilis
IM penicillin x1
Recheck nontreponemal titer for adequate response (4-fold decrease, eg, 1:16 to 1:4)

FIGURE 2.15-27. **Syphilis management algorithm.** (Reproduced with permission from USMLE-Rx.com.)

- **Primary/secondary:** Benzathine penicillin IM for one dose. Tetracycline or doxycycline for 14 days may be used for patients with penicillin allergy. Pregnant patients who are penicillin allergic and have ⊕ antibody titers must be desensitized and treated with penicillin.
- **Latent infection:** Treatment with benzathine penicillin. The physician should give one dose for early latent infection or a weekly dose for 3 weeks for late latent infection or for asymptomatic infection of unknown duration.
- **Neurosyphilis:** Treatment with penicillin IV for 10 to 14 days. Penicillin-allergic patients should be desensitized before therapy.

KEY FACT

Genital lesions caused by *Haemophilus ducreyi* ("do cry") and herpes lesions are painful. Syphi**lis** and the others are pain**less**.

KEY FACT

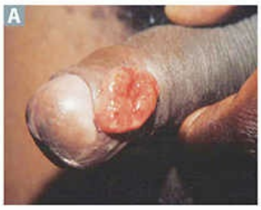
Regarding a patient with a nonhealing ulcerative lesion and inguinal lymphadenopathy with a ⊖ workup for a sexually transmitted infection (STI), think cancer.

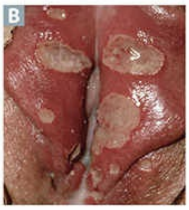
GENITAL LESIONS

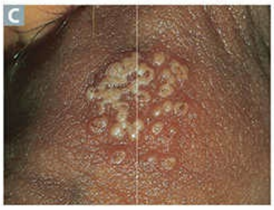
See Table 2.15-14 for a description of common sexually transmitted genital lesions along with an outline of their diagnosis and treatment.

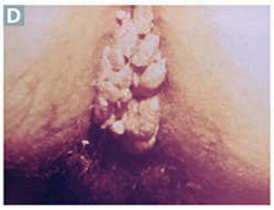
TABLE 2.15-14. Sexually Transmitted Genital Lesions

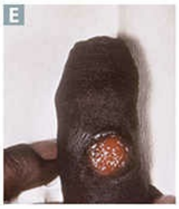
VARIABLE	KLEBSIELLA GRANULOMATIS[a] (GRANULOMA INGUINALE)	HAEMOPHILUS DUCREYI (CHANCROID)	HSV-1 OR HSV-2[b]	HUMAN PAPILLOMAVIRUS (HPV)[c]	TREPONEMA PALLIDUM (SYPHILIS)
Lesion	Papule becomes a beefy-red ulcer with a characteristic rolled edge of granulation tissue (see Image A)	Papule or pustule (chancroid; see Image B)	Vesicle (3–7 days postexposure; see Image C)	Papule (condylomata acuminata, warts; see Image D)	Papule (chancre; see Image E)
Appearance	Raised red lesions with a white border	Irregular, deep, well demarcated, necrotic	Regular, red, shallow ulcer	Irregular, pink or white, raised; like a cauliflower	Regular, red, round, raised
Number	One or multiple	1–3	Multiple	Multiple	Single
Size	5–10 mm	10–20 mm	1–3 mm	1–5 mm	1 cm
Pain	No	Yes	Yes	No	No
Concurrent signs and symptoms	Granulomatous ulcers	Inguinal lymphadenopathy	Malaise, myalgias, fever; vulvar burning; pruritus	Pruritus	Regional adenopathy
Diagnosis	Clinical examination, biopsy (Donovan bodies)	Difficult to culture; diagnosis made on clinical grounds, culture on specialized media	Tzanck smear showing multinucleated giant cells (best initial test); viral cultures (most accurate test); DFA or serology	Clinical exam; shave biopsy only if uncertain	Spirochetes seen under dark-field microscopy; *T pallidum* identified by serum antibody tests
Treatment[d]	Doxycycline or azithromycin	Single-dose azithromycin or ceftriaxone	Acyclovir, famciclovir, or valacyclovir for primary infection Foscarnet if resistant	Cryotherapy, laser, or excision; topical agents such as podophyllotoxin, imiquimod, or trichloroacetic acid	Penicillin IM











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[a] Previously known as *Calymmatobacterium granulomatis.*

[b] About 85% of genital herpes lesions are caused by HSV-2.

[c] HPV serotypes 6 and 11 are associated with genital warts; types 16, 18, and 31 are associated with cervical cancer.

[d] For all, treat sexual partners.

Image A reproduced with permission from Longo DL et al. *Harrison's Principles of Internal Medicine.* 18th ed. New York, NY: McGraw-Hill; 2012. Image B reproduced with permission from Wolff K, Johnson RA, Saavedra AP. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology.* 7th ed. New York, NY: McGraw-Hill; 2013. Image C reproduced with permission from Wolff K, Johnson R, Saavedra A. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology.* 7th ed. New York, NY: McGraw-Hill; 2013. Image D reproduced courtesy of Dr. Wiesner, Public Health Image Library, Centers for Disease Control and Prevention, Atlanta, GA. Image E reproduced courtesy of Public Health Image Library, Centers for Disease Control and Prevention, Atlanta, GA.

HIGH-YIELD FACTS IN

MULTISYSTEM

Shock

Fever
  POSTOPERATIVE FEVER
  FEVER OF UNKNOWN ORIGIN
  SEPSIS

Hematologic Infections
  MALARIA
  OTHER MOSQUITO-BORNE VIRUSES

Tick-Borne Infections
  LYME DISEASE
  BABESIOSIS
  ROCKY MOUNTAIN SPOTTED FEVER
  INFECTIOUS MONONUCLEOSIS

Human Immunodeficiency Virus
  VIRAL ANATOMY AND PATHOPHYSIOLOGY
  TRANSMISSION
  HIV SEROLOGY MONITORS DISEASE PROGRESSION
  OPPORTUNISTIC INFECTIONS IN HIV PATIENTS
  MANAGEMENT AND PREVENTION OF HIV
  IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME
  PROPHYLAXIS FOR OPPORTUNISTIC INFECTIONS AND VACCINATIONS
  CYTOMEGALOVIRUS

Central Line–Associated Bloodstream Infections

Thermal Dysregulation
  HYPOTHERMIA
  HYPERTHERMIA

Environment
  BURNS
  DROWNING
  HIGH-ALTITUDE SICKNESS
  BITES AND STINGS

Toxicology
  RESUSCITATION OF THE POISONED PATIENT
  HIGH-YIELD TOXICITIES
  COMMON DRUG INTERACTIONS AND REACTIONS
  MAJOR DRUG ADVERSE EFFECTS

Vitamin Deficiencies

Diseases Associated With Neoplasms

Trauma Management
- PRIMARY SURVEY
- SECONDARY SURVEY

Penetrating Trauma
- HEAD
- NECK
- CHEST
- ABDOMEN
- EXTREMITIES

Blunt and Deceleration Trauma
- HEAD AND FACE
- CHEST
- BLUNT CARDIAC INJURY
- ABDOMEN
- PELVIS

SHOCK

Defined as inadequate tissue-level oxygenation to maintain vital organ function. The multiple etiologies are differentiated by their cardiovascular effects and treatment options (see Table 2.16-1).

TABLE 2.16-1. Types of Shock

TYPE	MAJOR CAUSES	CARDIAC OUTPUT	PCWP	PVR	TREATMENT
Hypovolemic	Trauma, blood loss, dehydration with inadequate fluid repletion, third spacing, burns	↓	↓	↑	Replete with isotonic solution (eg, lactated Ringer's or normal saline) or blood; initiate blood transfusion in the setting of blood loss if blood pressure does not correct after addition of 2 L of isotonic crystalloid
Cardiogenic	CHF, arrhythmia, structural heart disease (severe mitral regurgitation, ventricular septal defect), MI >40% of left ventricular function)	↓	↑	↑	Identify the cause and treat if possible; give inotropic support; intra-aortic balloon pump may help
Obstructive	Cardiac tamponade, tension pneumothorax, massive pulmonary embolism	↓ ↓	↑ ↓	↑ ↑	Treat the underlying cause: pericardiocentesis, decompression of pneumothorax, and/or thrombolysis Equalization of pressures in all cardiac chambers distinguishes tamponade from other obstructive shock
Distributive		↑	↓	↓	
Septic	Any infection, but particularly common with bacteremia, especially gram ⊖ organisms				Administer broad-spectrum antibiotics Give crystalloid fluids up to 30 mL/kg ideal body weight Vasopressors (norepinephrine, vasopressin) may be needed if hypotension persists despite fluid resuscitation Obtain cultures before administration of antibiotics, when possible
Anaphylactic	Bee sting, medications, food allergy				Manage with 1:1000 epinephrine with potential adjuncts of H_1/H_2 antagonists and steroids
Systemic inflammatory response syndrome	Pancreatitis, burns, trauma				Manage underlying cause
Neurogenic	Brain or spinal cord injury				Maintain pressures with fluid and pressor support

CHF, Congestive heart failure; *H,* histamine; *MI,* myocardial infarction.

KEY FACT

Heart rate is the first vital sign to change in hemorrhagic shock. Blood pressure (BP) falls only after ≥1.5 L (30%–40% of blood volume) of blood loss.

FEVER

POSTOPERATIVE FEVER

Occurs in 40% of all postoperative patients. Timing after surgery determines the most likely cause (Fig. 2.16-1). Fever before day 3 is rarely of infectious origin. Table 2.16-2 summarizes the most common etiologies, based on postoperative day (POD) of onset.

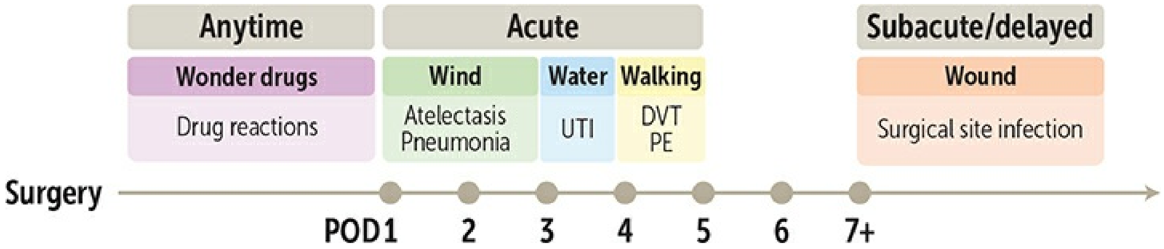


FIGURE 2.16-1. **Common causes of postoperative fever by timing.** The **5Ws** mnemonic can be used to remember the order of causes of postoperative fever. *POD*, Postoperative day. (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.16-2. **Postoperative Fever Timing**

TIMING	ETIOLOGY	PREVENTION	MNEMONIC
Any time	Drug reactions Examples: malignant hyperthermia (related to intraoperative anesthetics), antibiotics, blood product transfusion reactions	N/A	**W**onder drugs
Postoperative days 1–3	Atelectasis Pneumonia (day 3)	Incentive spirometry, early mobilization Antibiotics	**W**ind
PODs 3–4	Urinary tract infection	Short-term Foley catheter use	**W**ater
PODs 4–5	Deep venous thrombosis/pulmonary embolism	Early mobilization, heparin, sequential compression socks	**W**alking
PODs 7+	Surgical site infection	Dressing changes, preoperative antibiotics	**W**ound

KEY FACT

Endometritis is an additional cause of postoperative fever after C-section. Onset occurs anytime from POD 2 to 10.

KEY FACT

Immediate fever after administration of halothane or succinylcholine should raise concern for malignant hyperthermia. Assess for rigidity, metabolic acidosis, and electrolyte derangements. Treat with dantrolene and active cooling.

FEVER OF UNKNOWN ORIGIN

A temperature >38.3°C (100.9°F) of at least 3 weeks' duration that remains undiagnosed following three outpatient visits or 1 week of hospitalization.

KEY FACT

Overall, infections and cancer account for the majority (60%) of cases of fever of unknown origin. Autoimmune diseases account for ~15%. In older adults, rheumatic diseases account for one third of cases.

History/PE

Presents with fever. May complain of headache, myalgia, and malaise. The differential diagnosis includes the following:

- **Infectious:** Tuberculosis (TB), endocarditis (eg, HACEK organisms; see the Infective Endocarditis section in the Cardiovascular chapter), occult abscess (abdominal, prostatic), osteomyelitis, catheter infections, sinusitis. In HIV patients, consider Mycobacterium avium complex (MAC), histoplasmosis, and cytomegalovirus (CMV).
- **Neoplastic:** Lymphomas, leukemias, hepatic and renal cell carcinomas.
- **Autoimmune:** Still disease, systemic lupus erythematosus (SLE), cryoglobulinemia, polyarteritis nodosa, connective tissue disease, granulomatous disease (including sarcoidosis).
- **Miscellaneous:** Pulmonary emboli/deep venous thrombosis (DVT), inflammatory bowel disease (IBD), alcoholic hepatitis, drug fever, familial Mediterranean fever, factitious fever.
- Idiopathic (10%–15%).

Diagnosis

- Confirm the presence of fever and take a detailed history, including family, social, sexual, occupational, dietary, exposures (pets/animals), and travel.
- **Labs:** Obtain a complete blood cell count (CBC) with differential; erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP); serum protein electrophoresis; multiple blood cultures (similar to osteomyelitis workup); sputum Gram stain and culture; urinalysis (UA) and culture; and purified protein derivative (PPD). Complete appropriate cancer screening. Specific tests (antinuclear antibody [ANA], rheumatoid factor [RF], creatine kinase [CK], viral cultures, viral serologies/antigen tests) can be obtained if an infectious or autoimmune etiology is suspected.
- **Imaging:** Obtain a x-ray of the chest (CXR). CT of the chest, abdomen, and pelvis should be done early in the workup of a true fever of unknown origin (FUO). Invasive testing (marrow/liver biopsy) is generally low yield. Nuclear medicine and laparoscopy are higher yield as second-line tests (after CT).
- **Case by case**: Consider serologic testing for less common etiologies like *Brucella* spp., *Coxiella* spp., and *Bartonella* spp.

Treatment

Stop unnecessary medications. Remove indwelling lines or other potential sources of infection. Patients with FUO who have a completely ⊖ workup have a favorable prognosis, with fevers resolving over months to years.

SEPSIS

Sepsis is defined by organ dysfunction caused by a dysregulated host response to infection. Septic shock is essentially sepsis with associated profound metabolic, cellular, and circulatory disturbances that confer an increased risk of mortality.

History/PE

- Sepsis can be identified when there are signs of organ dysfunction in the setting of known or suspected infection. Clinical tools such as the sequential organ failure assessment (SOFA) or "quick" SOFA scores help identify and characterize dysfunction of several organ systems by noting the presence of tachycardia, altered mental status, and hypotension, among other findings.

- Septic shock is typically a "warm" shock, with warm skin and extremities. This contrasts with cardiogenic shock, which typically presents with cool skin and extremities.
- Petechiae, ecchymoses, and/or abnormal coagulation tests suggest disseminated intravascular coagulation (DIC; 2%–3% of cases).

Diagnosis

- Laboratory results frequently show leukocytosis or leukopenia with ↑ bands, thrombocytopenia (50% of cases), evidence of ↓ tissue perfusion (↑ creatinine, ↑ liver function tests [LFTs], ↑ lactate), and abnormal coagulation studies (↑ international normalized ratio [INR]). Hypotension requiring vasopressors to maintain mean arterial pressure (MAP) >65 mm Hg or persistently elevated lactate (>2 mEq/L) despite adequate fluid resuscitation diagnoses septic shock.
- It is critical to obtain cultures of all appropriate sites (eg, blood, sputum, cerebrospinal fluid [CSF], wound, urine). Obtaining cultures should not delay antibiotic administration.
- Imaging (CXR, CT) may aid in establishing the etiology or site of infection.

Treatment

- Intensive care unit (ICU) admission may be required. Treat aggressively with empiric antibiotics (based on the likely source of infection). Volume resuscitation with intravenous (IV) crystalloid and vasopressors should be used as needed to maintain adequate MAP (>65 mm Hg) and optimize end-organ perfusion.
- Treat underlying factors (eg, remove urinary catheter or infected lines, drain abscesses).

HEMATOLOGIC INFECTIONS

MALARIA

A protozoal disease caused by five species of the genus *Plasmodium* (*P falciparum*, *P vivax*, *P ovale*, *P malariae*, *P knowlesi*) and transmitted by the bite of an infected female *Anopheles* mosquito. *P falciparum* has the highest morbidity and mortality, occasionally within 24 hours of symptom onset. Travelers to endemic areas should take chemoprophylaxis and use mosquito repellent and bed nets to minimize exposure.

History/PE

- Patients have a history of exposure in a malaria-endemic area, with periodic attacks of sequential chills, fever (up to 41°C [105.8°F]), myalgias, headache, and diaphoresis occurring over 4 to 6 hours.
- Splenomegaly often appears 4 or more days after symptom onset. Patients are often asymptomatic between attacks, which recur every 2 to 3 days, depending on the *Plasmodium* species involved.
- Severely ill patients may present with hyperpyrexia, prostration, impaired consciousness, pulmonary edema, acidosis, hyperventilation, and bleeding. The presence of a rash, skin ulcer, eosinophilia, lymphadenopathy, neck stiffness, or photophobia suggests a different

or additional diagnosis.

Diagnosis

- Timely diagnosis of the correct species is essential because *P falciparum* can be fatal and is often resistant to standard chloroquine treatment.
- The physician should send Giemsa- or Wright-stained thick and thin blood films for evaluation to detect *Plasmodium* and determine the species type, respectively, and the degree of parasitemia (see Fig. 2.16-2).

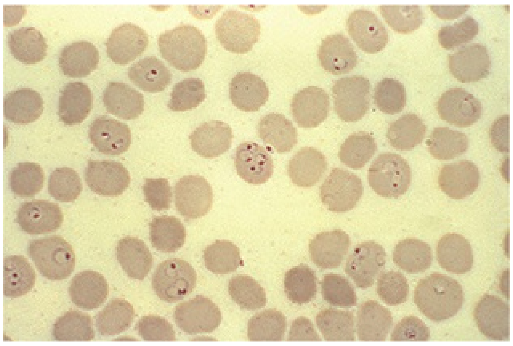


FIGURE 2.16-2. ***Plasmodium falciparum* hyperparasitemia in the thin smear of a patient with cerebral malaria.** (Reproduced with permission from the US Department of Health and Human Services and Steven Glenn.)

- CBC usually demonstrates normochromic, normocytic anemia, with reticulocytosis and thrombocytopenia early in the disease.
- If resources allow, more sensitive serologic tests are available, including rapid antigen detection methods, fluorescent antibody methods, and polymerase chain reaction (PCR).
- In patients with altered mental status, the physician should obtain a fingerstick glucose to rule out hypoglycemia.

KEY FACT

Cerebral malaria presents with headache, altered mental status, neurologic signs, retinal hemorrhages, convulsions, and delirium. If left untreated, it can rapidly progress to coma and death.

Treatment

- Uncomplicated malarial infection can be treated with oral agents. Chloroquine has historically been the standard antimalarial medication, but high resistance rates often necessitate the use of other medications such as mefloquine, atovaquone-proguanil, or artemisinins (for severe cases).
- In cases of *P vivax*, *P ovale,* or an unknown species, primaquine is added to eradicate the hypnozoites in the liver.
- For patients traveling to endemic regions, the physician should prescribe prophylaxis consisting of atovaquone-proguanil or mefloquine given at least 2 weeks before travel and continued for 4 weeks after returning.

KEY FACT

Antimalarial contraindications:

- Primaquine: Requires testing for G6PD first
- Mefloquine: Seizure, psychiatric conditions, and cardiac conduction disorders
- Atovaquone/proguanil: Pregnancy/breastfeeding, renal disease
- Chloroquine: Psoriasis

Complications

Cerebral malaria, severe hemolytic anemia, renal impairment, noncardiogenic pulmonary edema, hypoglycemia, lactic acidosis, acute hepatopathy, and gram ⊖ bacteremia.

OTHER MOSQUITO-BORNE VIRUSES

The following viruses are carried by the *Aedes* mosquito and present with rash, fever, and myalgias:

- **Chikungunya:** Notably causes joint pain. Supportive care is the treatment.
- **Dengue (“breakbone fever”):** Presents with bone pain and can be complicated by severe thrombocytopenia, bleeding, and shock. Findings of low WBCs and ↑ LFTs. Treatment calls for fluids and blood products as needed.
- **Zika:** Flavivirus that causes conjunctivitis and headache. Associated with Guillain-Barré syndrome. It can cause microcephaly of the fetus if the patient is infected during pregnancy. Treatment is supportive care.

TICK-BORNE INFECTIONS

LYME DISEASE

A tick-borne disease caused by the spirochete *Borrelia burgdorferi*. Usually seen during the summer months and carried by *Ixodes* ticks on white-tailed deer and white-footed mice. Endemic to the Northeast, northern Midwest, and Pacific coast.

KEY FACT

Ehrlichiosis is a disease transmitted by the lone star tick endemic to the south-central and southeastern United States. It causes headache, fever, chills, altered mental status, and myalgias, but rash is uncommon. Leukopenia, thrombocytopenia, and ↑ liver enzymes are common laboratory findings. Doxycycline is the treatment of choice.

History/PE

- Presents at the onset of rash with fever, malaise, fatigue, headache, myalgias, and/or arthralgias. Infection usually occurs after a tick feeds for >36 hours.
- **Primary (early localized disease):** Erythema migrans begins as a small erythematous macule or papule that is found at the tick-feeding site and expands slowly over days to weeks. The border may be macular or raised, often with central clearing (“bull’s-eye”; see Fig. 2.16-3).

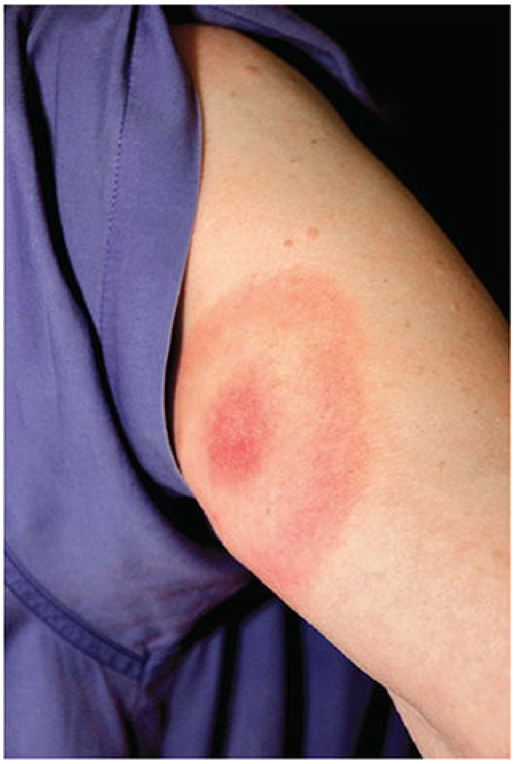


FIGURE 2.16-3. **Erythema chronicum migrans seen in Lyme disease.** Note the classic "bull's-eye" lesion, which consists of an outer ring where the spirochetes are found, an inner ring of clearing, and central erythema caused by an allergic response at the site of the tick bite. (Reproduced with permission from the US Department of Health and Human Services and James Gathany.)

- **Secondary (early disseminated disease):** Presents with migratory polyarthropathies, neurologic phenomena (eg, facial nerve palsy; bilateral is classic for Lyme disease), lymphocytic meningitis and/or myocarditis, and conduction abnormalities (third-degree heart block).
- **Tertiary (late disease):** Arthritis and subacute encephalitis (memory loss and mood change).

Diagnosis

- Early Lyme disease is diagnosed on clinical presentation alone (erythema migrans + endemic area). Serologic tests are not required or recommended, as IgM becomes ⊕ 1 to 2 weeks, and IgG 2 to 6 weeks, after onset of erythema migrans.
- Early disseminated or late Lyme disease presenting with consistent symptoms and exposure risk factors should be diagnosed with serology. If enzyme-linked immunosorbent assay (ELISA) IgM and IgG are ⊕ or equivocal, then Western blot can be used for confirmation. Western blot should not be used for "screening" or nonspecific symptoms. Western blots sent without ELISA have high false ⊕ rates.

Treatment

- If the tick is still attached, remove it with forceps and thoroughly disinfect the area. Treat early disease with doxycycline (or amoxicillin in pregnant patients). Short courses of doxycycline may be used in young patients. More advanced disease (eg, central nervous system [CNS], cardiac, or arthritic disease) should be treated with ceftriaxone.
- Consider empiric therapy for patients with the characteristic rash, arthralgias, or a tick bite acquired in an endemic area. Prevent with tick bite avoidance.

- Prophylaxis: Give one dose of doxycycline if all of the following apply: tick is *Ixodes scapularis* and has been attached for ≥36 hours, prophylaxis is started ≤72 hours of removal, patient has no contraindications to doxycycline, and local rate of infection of ticks with *B burgdorferi* is >20%. **If criteria are not met, observe and treat only if erythema migrans develops.**

KEY FACT

"Tick testing" is a common incorrect answer choice; it has no effect on management and is not performed in a Lyme disease workup.

BABESIOSIS

Tick-borne protozoal illness also transmitted by *I scapularis* (high rate of coinfection with Lyme disease). Causes flulike symptoms, intravascular hemolysis, anemia, and jaundice. Ring-shaped or "Maltese cross" organisms may be seen on blood smear. Can become severe if risk factors are present (eg, asplenia, immunocompromise, or malignancy). Treat with oral azithromycin (IV if severe) and atovaquone.

ROCKY MOUNTAIN SPOTTED FEVER

A disease caused by *Rickettsia rickettsii* and carried by the American dog tick (*Dermacentor variabilis*). Cases are most common during June and July and in Midwestern and Eastern states (Arkansas, Missouri, Virginia, and North Carolina). The organism invades the endothelial lining of capillaries and causes small vessel vasculitis.

- ***Hx/PE:*** Presents with headache, fever, malaise, and rash. The characteristic rash is initially macular (beginning on the wrists and ankles) but becomes petechial/purpuric as it spreads centrally (see Fig. 2.16-4). Altered mental status or DIC may develop in severe cases.

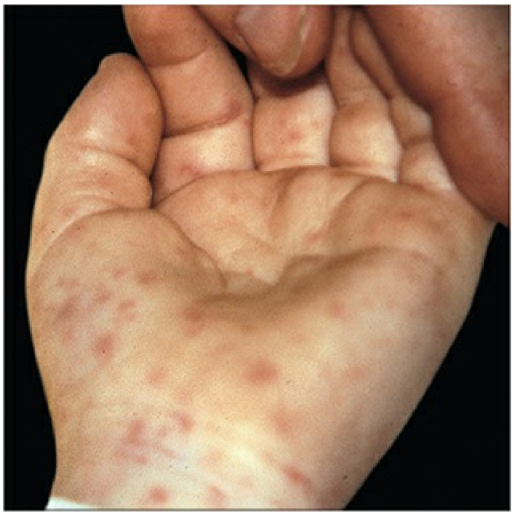


FIGURE 2.16-4. **Rocky Mountain spotted fever.** These erythematous macular lesions will evolve into a petechial rash that will spread centrally. (Reproduced with permission from Wolff K, Johnson RA, Saavedra AP. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 7th ed. New York, NY: McGraw-Hill; 2013.)

- ***Dx:*** Clinical diagnosis should be confirmed with biopsy and indirect immunofluorescence of the skin lesion.
- ***Tx:*** Empiric therapy with doxycycline. The condition can be rapidly fatal if left untreated. If clinical suspicion is high, treatment should begin while awaiting testing. Chloramphenicol can be used during the first two trimesters of pregnancy in uncomplicated cases, but if it is not available, doxycycline therapy should be initiated.

KEY FACT

Rocky Mountain spotted fever starts on the wrists and ankles and then spreads centrally.

INFECTIOUS MONONUCLEOSIS

Most commonly occurs in young adult patients; usually caused by acute Epstein-Barr virus (EBV) infection. Transmission most often occurs through exchange of body fluids, most commonly saliva.

History/PE

- Presents with fever and pharyngitis. Fatigue invariably accompanies initial the illness and may persist for 3 to 6 months. Examination may reveal low-grade fever, generalized lymphadenopathy (especially posterior cervical), tonsillar exudate and enlargement, palatal petechiae, a generalized maculopapular rash, splenomegaly, and bilateral upper eyelid edema. Symptoms appear 2 to 5 weeks after infection.
- In older children and adults, it may cause mesenteric lymphadenitis, mimicking appendicitis.
- Patients who present with pharyngitis as their primary symptom may be misdiagnosed with streptococcal pharyngitis (30% of patients with infectious mononucleosis are asymptomatic carriers of group A streptococcus [GAS] in their oropharynx).
- The differential diagnosis includes CMV, toxoplasmosis, HIV, human herpesvirus (HHV) 6, other causes of viral hepatitis, and lymphoma.

Diagnosis

- **Best initial test:** Heterophile antibody (Monospot) test. It may be ⊝ in the first few weeks after symptoms begin.
- An EBV-specific antibody test can be ordered in patients with suspected mononucleosis and a ⊝ Monospot test. Infectious mononucleosis syndromes with a ⊝ Monospot test and ⊝ EBV antibody are most often caused by CMV infection. Acute HIV and other viral etiologies should be considered.
- CBC with differential often reveals mild thrombocytopenia with relative lymphocytosis and >10% atypical T lymphocytes.
- A comprehensive metabolic panel usually reveals mildly elevated transaminases, alkaline phosphatase, and total bilirubin.

KEY FACT

Lymphocytosis in EBV infection is predominantly caused by B-cell proliferation, but the atypical cells are T lymphocytes.

Treatment

Treatment is supportive, as there is no effective antiviral therapy. Corticosteroids are indicated for airway compromise caused by tonsillar enlargement, severe thrombocytopenia, or severe autoimmune hemolytic anemia.

Complications

- **CNS infection:** Can present as aseptic meningitis, encephalitis, meningoencephalitis, cranial nerve palsies (particularly cranial nerve [CN] VII), optic and peripheral neuritis, transverse myelitis, or Guillain-Barré syndrome.
- **Splenic rupture:** Occurs in <0.5% of cases. More common in males. Presents with abdominal pain, referred left shoulder pain, and/or hemodynamic compromise. Patients should avoid contact sports for at least 4 weeks to prevent this complication.
- **Upper airway obstruction:** Treatment with steroids.
- **Bacterial superinfection:** Can lead to development of a secondary streptococcal pharyngitis.
- **Fulminant hepatic necrosis:** More common in males; the most common cause of death in affected males.
- **Autoimmune hemolytic anemia:** Occurs in 2% of patients during the first 2 weeks. Coombs ⊕. Mild anemia lasts 1 to 2 months. If severe, treatment calls for corticosteroids.
- **Nasopharyngeal carcinoma:** Presents with epistaxis, headache, and cervical lymph node spread; especially prevalent in Southeast Asia.

KEY FACT

Patients with mononucleosis who are given ampicillin for suspected streptococcal pharyngitis may develop a prolonged, pruritic maculopapular rash.

HUMAN IMMUNODEFICIENCY VIRUS

A positive-sense diploid RNA genome retrovirus that preferentially targets and destroys CD4+ T cells, leading to immunosuppression (see Fig. 2.16-5). Transmission occurs via any activity that shares infected body fluids (blood, semen, vaginal fluids). Receptive anal sex without condom use has the greatest risk of transmission due to tearing of anal mucosa + sharing of bodily fluids. Men who have sex with men (MSM) account for the greatest number of new HIV diagnoses in the United States, with disproportionately higher rates among Black MSM. Worldwide, however, heterosexual transmission accounts for the greatest number of cases.

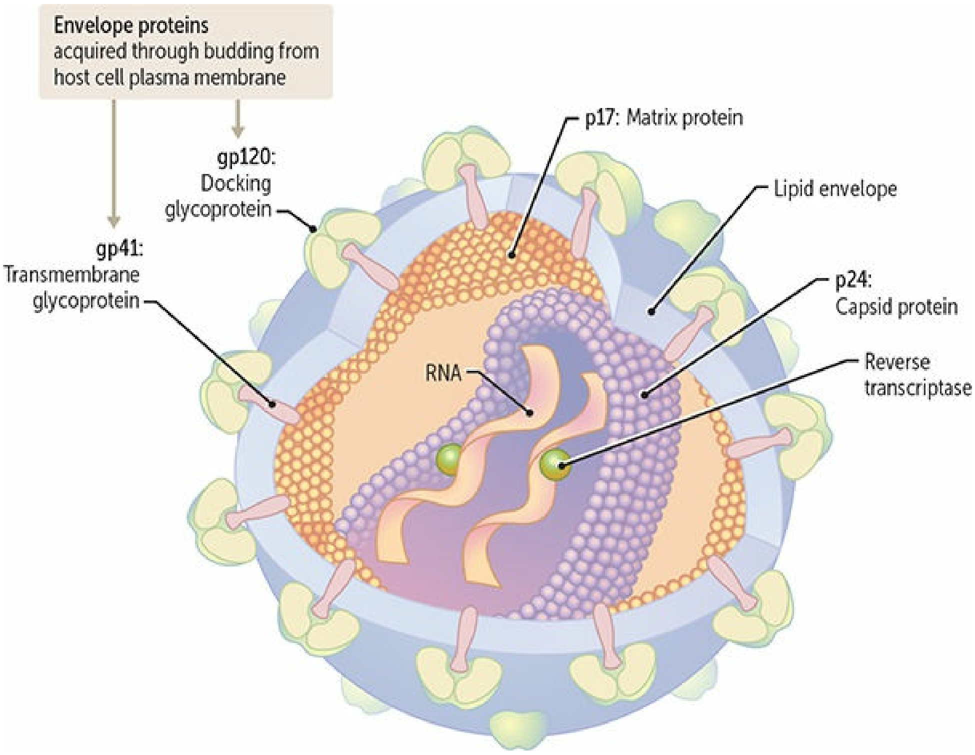

Envelope proteins
acquired through budding from
host cell plasma membrane
gp120:
Docking
glycoprotein
gp41:
Transmembrane
glycoprotein
p17: Matrix protein
Lipid envelope
p24:
Capsid protein
Reverse
transcriptase
RNA

FIGURE 2.16-5. **Viral anatomy.** (Reproduced with permission from USMLE-Rx.com.)

VIRAL ANATOMY AND PATHOPHYSIOLOGY

Diploid genome (two molecules of RNA). The three structural genes (protein coded for):

- *env* (gp120 and gp41):
  - Formed from cleavage of gp160 to form envelope glycoproteins
  - gp120—attachment to host CD4+ T cell
  - gp41—fusion and entry
- *gag* (p24 and p17)—capsid and matrix proteins, respectively
- pol—reverse transcriptase, integrase, protease; RIP “Pol” (Paul)

Reverse transcriptase synthesizes double-stranded DNA (dsDNA) from genomic RNA; dsDNA integrates into host genome.

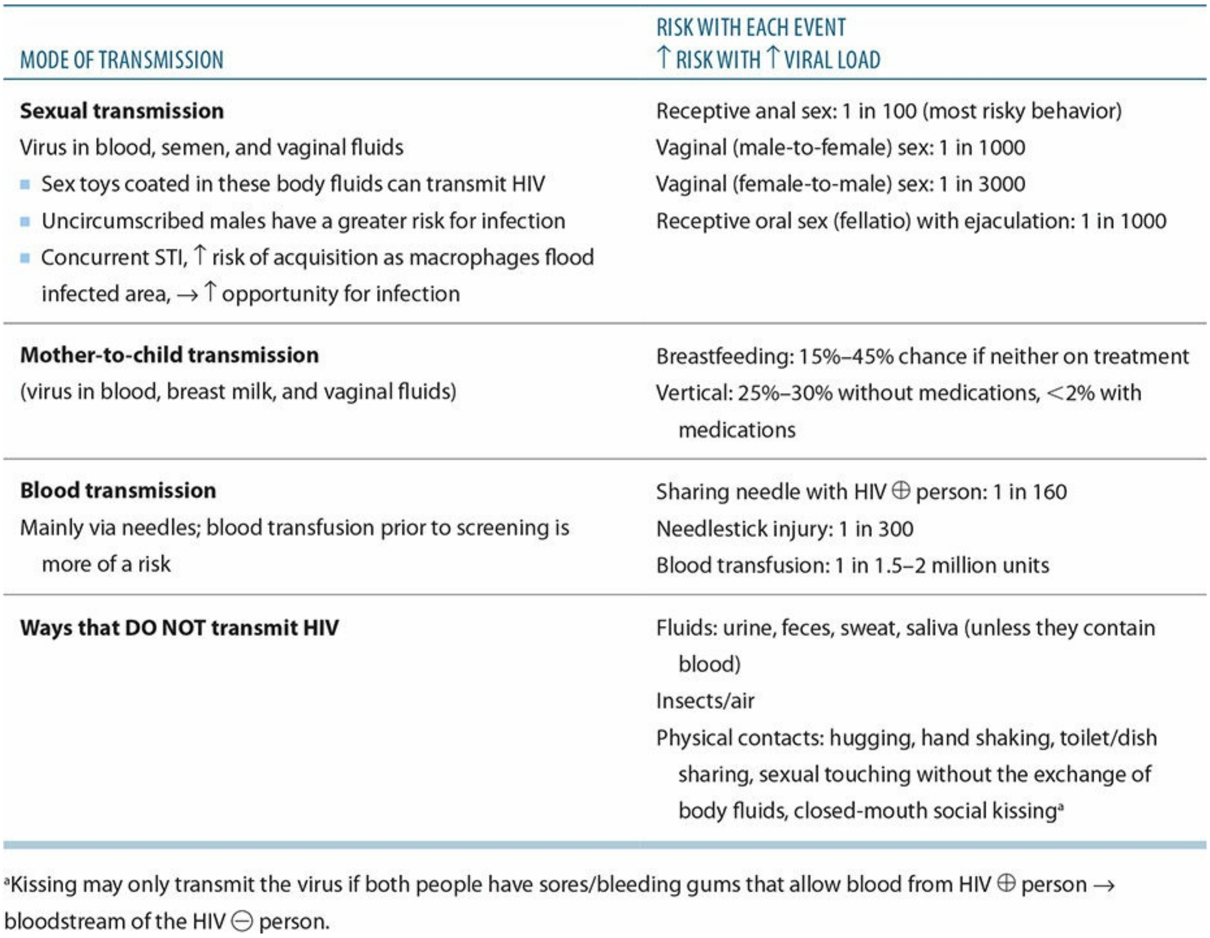
Virus binds CD4 as well as a coreceptor, either CCR5 on macrophages (early infection) or CXCR4 on T cells (late infection).

Homozygous CCR5 mutation = immunity. Heterozygous CCR5 mutation = slower course.

TRANSMISSION

HIV can be transmitted both vertically (mother to child) and horizontally (through sexual intercourse and contaminated blood) (Table 2.16-3).

TABLE 2.16-3. **Risk of HIV Transmission Without Prophylactic Treatment**



MODE OF TRANSMISSION	RISK WITH EACH EVENT ↑ RISK WITH ↑ VIRAL LOAD
Sexual transmission Virus in blood, semen, and vaginal fluids - Sex toys coated in these body fluids can transmit HIV - Uncircumscribed males have a greater risk for infection - Concurrent STI, ↑ risk of acquisition as macrophages flood infected area, → ↑ opportunity for infection	Receptive anal sex: 1 in 100 (most risky behavior) Vaginal (male-to-female) sex: 1 in 1000 Vaginal (female-to-male) sex: 1 in 3000 Receptive oral sex (fellatio) with ejaculation: 1 in 1000
Mother-to-child transmission (virus in blood, breast milk, and vaginal fluids)	Breastfeeding: 15%–45% chance if neither on treatment Vertical: 25%–30% without medications, <2% with medications
Blood transmission Mainly via needles; blood transfusion prior to screening is more of a risk	Sharing needle with HIV ⊕ person: 1 in 160 Needlestick injury: 1 in 300 Blood transfusion: 1 in 1.5–2 million units
Ways that DO NOT transmit HIV	Fluids: urine, feces, sweat, saliva (unless they contain blood) Insects/air Physical contacts: hugging, hand shaking, toilet/dish sharing, sexual touching without the exchange of body fluids, closed-mouth social kissing[a]

[a] Kissing may only transmit the virus if both people have sores/bleeding gums that allow blood from HIV ⊕ person → bloodstream of the HIV ⊖ person.

HIV SEROLOGY MONITORS DISEASE PROGRESSION

- **CD4+ cell count:** Best indicator of immunosuppression, risk for disease progression, and opportunistic infections (OIs). Guides OI prophylaxis and assesses response to antiretroviral therapy (ART).
- **Viral load:** Assesses response to ART and provides prognostic information.

History/PE

Depends on stage of infection (see Fig. 2.16-6).

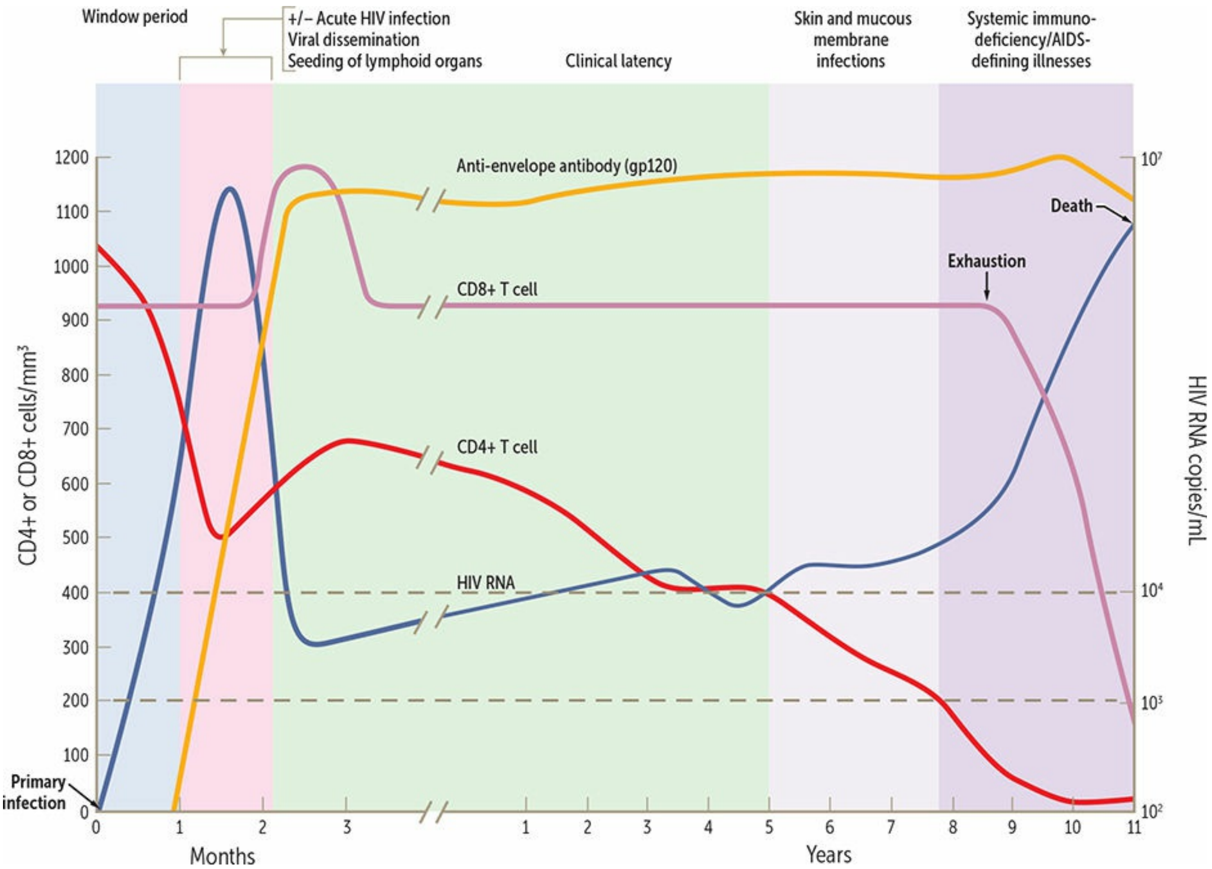


FIGURE 2.16-6. **Time course of HIV infection.** Note that the level of CD4+ cells remains normal for many years but then declines, resulting in the immunodeficiency stage, which is characterized by opportunistic infections and malignancies. (Reproduced with permission from USMLE-Rx.com.)

- **Acute HIV:** Initial infection is asymptomatic in 10% to 60% of cases. If symptomatic, the acute HIV syndrome occurs 2 to 4 weeks after exposure and presents as a mononucleosis-type syndrome (suspect HIV in person with sexually transmitted infection [STI] risk factors) and/or a flulike syndrome. Symptoms may include fever, sore throat, cervical lymphadenopathy, maculopapular rash, headache, painful mucocutaneous ulcers, and gastrointestinal (GI) symptoms. Notably, the viral RNA load is elevated, but seroconversion has not yet occurred (antibodies nonreactive).
- **Chronic (clinically latent) HIV:** Can be asymptomatic for a period of 8 to 10 years. Persistent generalized lymphadenopathy may be present along with fatigue. Notably, *Candida* infections of thrush or vaginitis in a patient with risk factors for STIs should raise clinical suspicion for HIV (see Fig. 2.16-7). Seborrheic dermatitis is also a common finding in this stage. Overall, the CD4+ T-cell count progressively declines over multiple years in this phase. The latency of this phase is why screening is recommended (see later diagnosis section).

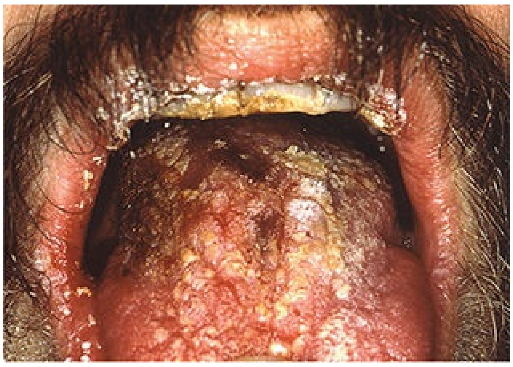


FIGURE 2.16-7. **Oral thrush in HIV-positive patient.** (Reproduced with permission from Drs. John Molinari and Sol Silverman, Jr., Centers for Disease Control and Prevention, Atlanta, GA.)

- **AIDS:** The average time, in the absence of treatment, from exposure → AIDS is 8 years. Defined as a CD4+ T-cell count <200/mm^3 or an AIDS-defining infection. Clinical presentations vary and are due to opportunistic infections.
- Dashed lines on CD4+ cell count axis indicate moderate immunocompromise (<400 CD4+ cells/mm^3) and when AIDS-defining illnesses emerge (<200 CD4+ cells/mm^3).
- Most patients who do not receive treatment eventually die of complications of HIV infection.
- **F**our stages of untreated infection:
  1. **F**lulike (acute)
  2. **F**eeling fine (latent)
  3. **F**alling count
  4. **F**inal crisis
- During the clinical latency phase, the virus replicates in lymph nodes.

Diagnosis

See Figure 2.16-8 for steps in the laboratory diagnosis.

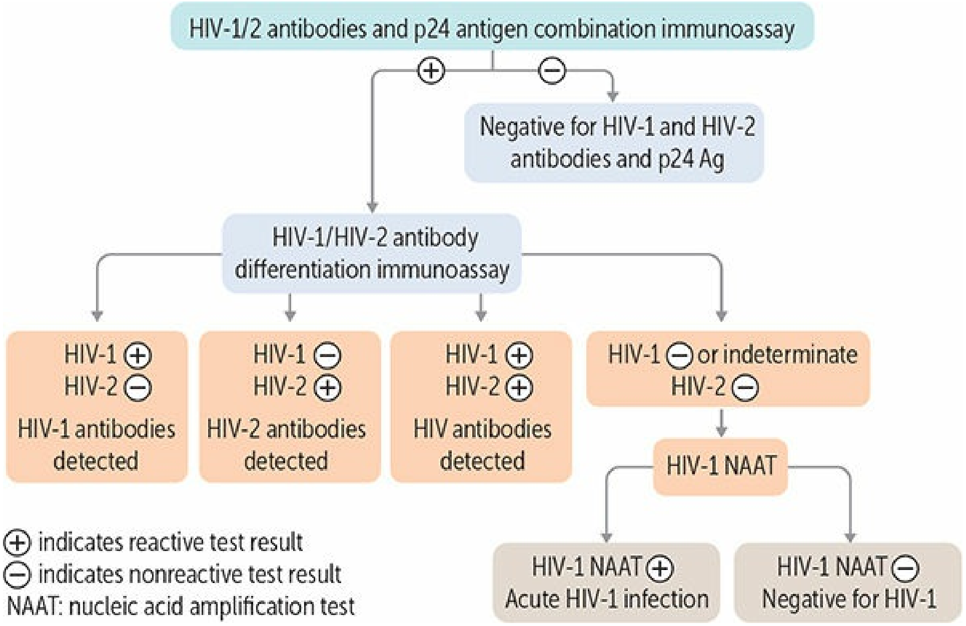

HIV-1/2 antibodies and p24 antigen combination immunoassay
⊕
⊖
Negative for HIV-1 and HIV-2 antibodies and p24 Ag
HIV-1/HIV-2 antibody differentiation immunoassay
HIV-1 ⊕ HIV-2 ⊖ HIV-1 antibodies detected
HIV-1 ⊖ HIV-2 ⊕ HIV-2 antibodies detected
HIV-1 ⊕ HIV-2 ⊕ HIV antibodies detected
HIV-1 ⊖ or indeterminate HIV-2 ⊖
HIV-1 NAAT
HIV-1 NAAT ⊕ Acute HIV-1 infection
HIV-1 NAAT ⊖ Negative for HIV-1
⊕ indicates reactive test result
⊖ indicates nonreactive test result
NAAT: nucleic acid amplification test

FIGURE 2.16-8. **Scheme for laboratory diagnosis of HIV.** (Reproduced with permission from USMLE-Rx.com.)

- **Best initial test:** Combination antigen/antibody test (fourth-generation test). Detects p24 antigen (major capsid protein) + anti-HIV antibodies. ⊕ result if antigen OR antibodies detected. Identifies virus ~2 weeks postinfection.
- **Confirmatory test:** HIV-1/2 differentiation immunoassay (preferred over Western blot). HIV type guides treatment. HIV-1: More common and found worldwide. HIV-2: Mainly in West Africa.
- **Special testing scenarios:**
  - **Early acute HIV:** A combination test (may not be ⊕ until ~2 weeks postinfection) AND a viral RNA load (PCR-RNA)
  - **Perinatal HIV:** Maternal HIV antibodies (Abs) → newborn (cannot use Ab tests); use nucleic acid tests
- **AIDS:** HIV and one or more of the following:
  - CD4+ T-cell count $<200/\text{mm}^3$
  - CD4+ T-cell percentage of total lymphocytes <14%
  - AIDS-defining illness

Screening

Indications:

- One-time screening with a combined test for all adolescents and adults aged 15 to 64 years
- Annual screening for high-risk patients: IV drug users and partners, sex workers, sex partners of HIV ⊕ people or high-risk partners, MSM
- Routine prenatal screening, people with new STIs, exposure to possibly infected body fluids

OPPORTUNISTIC INFECTIONS IN HIV PATIENTS

↓ CD4+ cell count → reactivation of past infections (eg, TB, herpes simplex virus [HSV], shingles), dissemination of bacterial infections and opportunistic fungal infections (eg, coccidioidomycosis), and non-Hodgkin lymphomas (Table 2.16-4). The risk of OIs in HIV ⊕ adults directly correlates with the CD4+ cell count (Fig. 2.16-9).

TABLE 2.16-4. **Opportunistic Infections in HIV Patients**

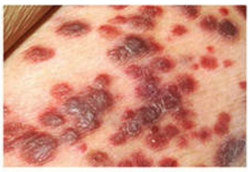
PATHOGEN	PRESENTATION	FINDINGS
CD4+ CELL COUNT $<500/\text{MM}^3$		
Candida albicans	Oral thrush	Scrapable white plaque, pseudohyphae on microscopy
EBV	Oral hairy leukoplakia	Unscrapable white plaque on lateral tongue
Human herpesvirus (HHV)-8 	Kaposi sarcoma	Perivascular spindle cells invading and forming vascular tumors on histology
Human papillomavirus (HPV)	Squamous cell carcinoma at sites of sexual contact (most commonly anus, cervix, oropharynx)	Koilocytic change noted on microscopy
Mycobacterium Tuberculosis	Increased risk of reactivation of latent TB infection	Pulmonary and extrapulmonary findings; presence of acid-fast bacilli on microscopy
CD4+ CELL COUNT $<200/\text{MM}^3$		
Histoplasma Capsulatum	Fever, weight loss, fatigue, cough, dyspnea, nausea, vomiting, diarrhea	Oval yeast cells within macrophages
HIV	Dementia, HIV-associated nephropathy	Cerebral atrophy on neuroimaging
JC virus (reactivation)	Progressive multifocal leukoencephalopathy	Nonenhancing areas of demyelination on MRI
Pneumocystis jirovecii	*Pneumocystis* pneumonia	"Ground-glass" opacities on chest imaging
CD4+ CELL COUNT $<100/\text{MM}^3$		
Bartonella spp.	Bacillary angiomatosis	Multiple red to purple papules or nodules Biopsy with neutrophilic inflammation
Candida albicans	Esophagitis	White plaques on endoscopy; yeast and pseudohyphae on biopsy
CMV	**C**olitis, **R**etinitis, **E**sophagitis, **E**ncephalitis, **P**neumonitis (**CREEP**)	Linear ulcers on endoscopy, cotton-wool spots on fundoscopy Biopsy revealing cells with intranuclear (owl's eye) inclusion bodies
Cryptococcus neoformans	Meningitis	Encapsulated yeast on India ink stain or capsular antigen ⊕
Cryptosporidium spp.	Chronic, watery diarrhea	Acid-fast oocysts in stool
EBV	B-cell lymphoma (eg, non-Hodgkin lymphoma, CNS lymphoma)	CNS lymphoma—ring enhancing, may be solitary (vs *Toxoplasma*)
Mycobacterium avium–intracellulare, Mycobacterium avium complex	Nonspecific systemic symptoms (fever, night sweats, weight loss) or focal lymphadenitis	Most common if CD4+ cell count $<50/\text{mm}^3$
Toxoplasma gondii	Brain abscesses	Multiple ring-enhancing lesions on MRI

Image reproduced with permission from the National Cancer Institute.

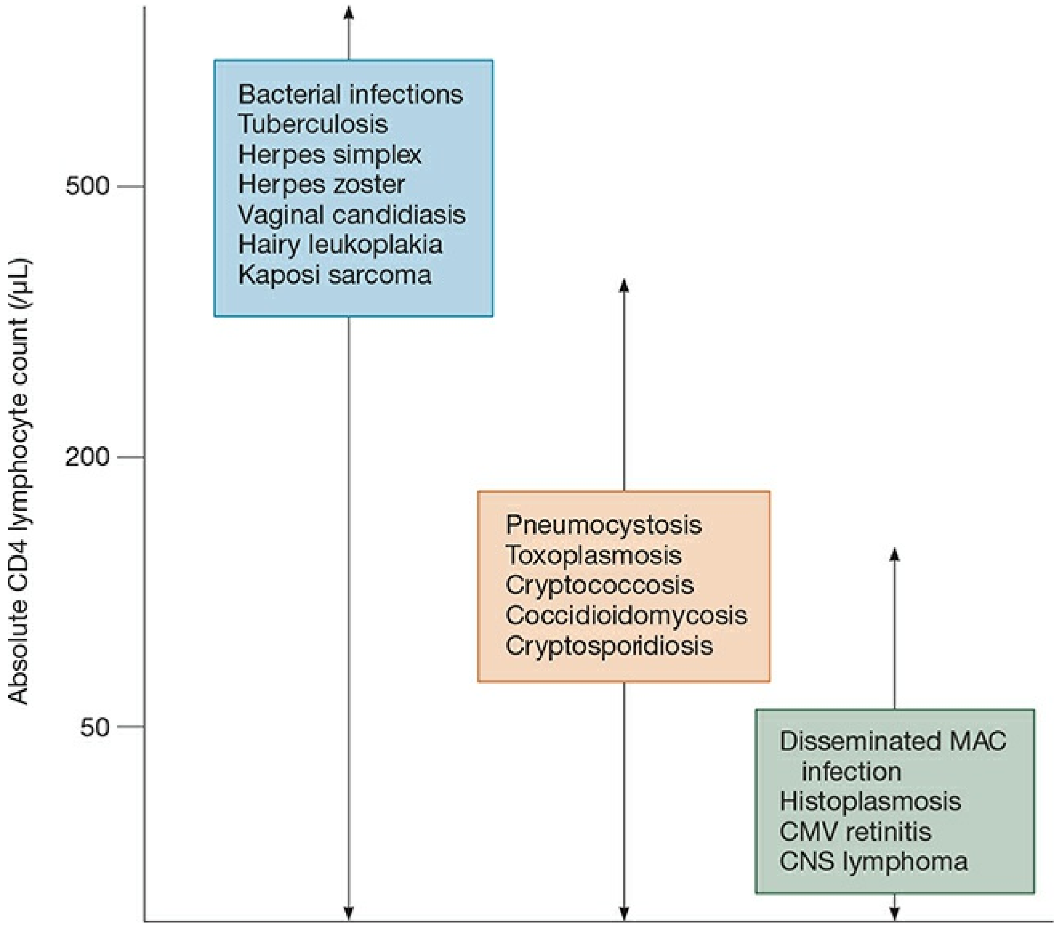


FIGURE 2.16-9. **Relationship of CD4+ cell count to development of opportunistic infections.** (Reproduced with permission from USMLE-Rx.com.)

MANAGEMENT AND PREVENTION OF HIV

ART:

- Lifelong ART is prescribed for all HIV ⊕ patients, even during pregnancy, regardless of CD4+ cell count. Counseling about strict (100%) adherence is crucial, as minor regimen deviations → resistance.
- Viral resistance testing (genotyping) should be performed prior to ART initiation AND if there is evidence of treatment failure (see viral load information). Both enable a more tailored regimen to be prescribed.
- Viral load (PCR-RNA) and CD4+ T-cell count are measured at time of diagnosis and then every 3 to 4 months.
- Monitoring viral load (PCR-RNA levels) serves two main purposes:
  - Measures response to therapy: ↑ or >50/µL (after 4 months of treatment) viral RNA = evaluation for regimen change; ↓/undetectable (treatment goal defined as <20/µL) viral RNA = continue therapy
  - Assesses treatment as prevention: Undetectable (goal <20/µL) viral RNA = ↓↓↓↓ transmission risk
- Initial regimens generally consist of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus one integrase inhibitor (which are superior to, but can be substituted by, a non-nucleoside RTI [NNRTI] or protease inhibitor, depending on the specific patient’s needs). Triple-drug ART regimens are referred to as highly active

antiretroviral therapy (HAART). Used to prevent viral resistance. See Figure 2.16-10 for targets of therapy and Table 2.16-5 for drug classes, agents, mechanisms of action, and adverse effects.

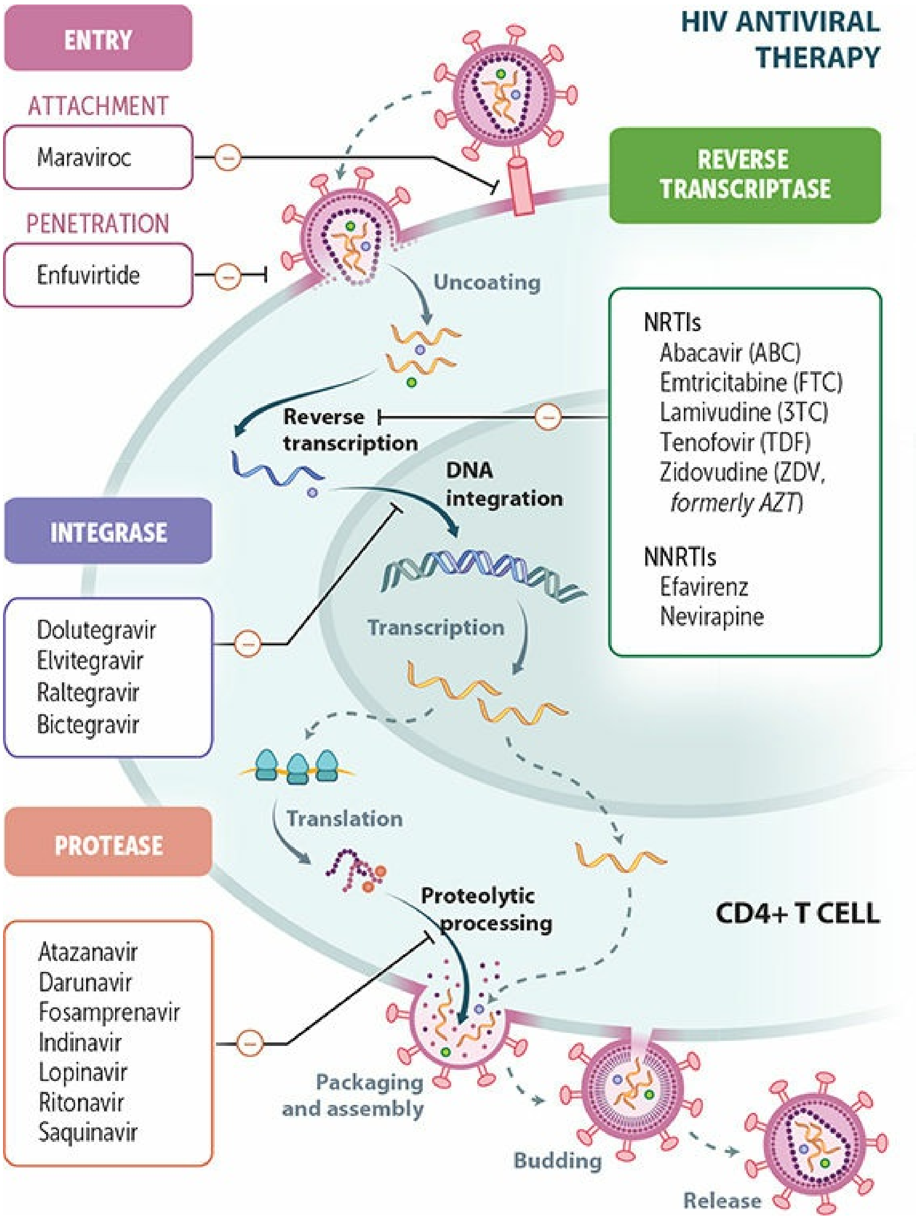

HIV ANTIVIRAL THERAPY
ENTRY
ATTACHMENT
Maraviroc
PENETRATION
Enfuvirtide
REVERSE TRANSCRIPTASE
Uncoating
NRTIs
Abacavir (ABC)
Emtricitabine (FTC)
Lamivudine (3TC)
Tenofovir (TDF)
Zidovudine (ZDV, formerly AZT)
NNRTIs
Efavirenz
Nevirapine
Reverse transcription
DNA integration
INTEGRASE
Dolutegravir
Elvitegravir
Raltegravir
Bictegravir
Transcription
Translation
PROTEASE
Atazanavir
Darunavir
Fosamprenavir
Indinavir
Lopinavir
Ritonavir
Saquinavir
Proteolytic processing
CD4+ T CELL
Packaging and assembly
Budding
Release

FIGURE 2.16-10. **Molecular targets of HIV antiretroviral therapy.** (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.16-5. **Antiretroviral Therapy Classes, Agents, Mechanisms of Actions, and Adverse Effects (see Fig. 2.16-10)**

CLASS	AGENTS	MECHANISM OF ACTION	ADVERSE EFFECTS
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	Nucleosides: Abacavir (ABC), didanosine (ddI), emtricitabine (FTC), lamivudine (3TC), stavudine (d4T), zalcitabine (ddC), zidovudine (ZDV, formerly AZT) Nucleo**T**ide: **T**enofovir in two formulations Tenofovir disoproxil fumarate (TDF), which is associated with kidney injury and bone loss Tenofovir alafenamide (TAF), which has ↓ adverse effects	All nucleosides must be phosphorylated to their active nucleotide form (except tenofovir) to competitively inhibit reverse transcriptase (drugs lack 3′-OH group vs endogenous nucleotides) → prevent DNA chain elongation → DNA chain termination	NRTIs inhibit DNA polymerase gamma → mitochondrial toxicity → lactic acidosis, ↑ CK myopathy, peripheral neuropathy (ddI, d4T), pancreatitis (ddI), hepatic steatosis, lipoatrophy (stavudine, ZDV) Bone marrow suppression and megaloblastic anemia (ZDV) Abacavir hypersensitivity (human leukocyte antigen [HLA]-B*5701) fever, rash, GI symptoms

Non-nucleoside/ nucleotide reverse transcriptase inhibitors (NNRTIs)	Efavirenz Contraindicated in pregnancy Does NOT interfere with TB medications = one clinical scenario where drug is preferred. Delavird**ine** (contraindicated in pregnancy) Nevirap**ine**, rilpivir**ine** Entire class: Not active against HIV-2	Does NOT require phosphorylation to become active Allosteric binding to reverse transcriptase → enzyme confirmational change → non-competitive inhibition	Hepatotoxic and varying ↑↓ CYP450 Metabolism, rash, and Stevens-Johnson syndrome (SJS) Teratogenic (efavirenz, delavirdine) CNS toxicity (efavirenz, rilpivirine): Vivid dreams, insomnia, mood changes, confusion, anxiety, depression
Integrase stand transfer inhibitors	Common **-tegravir** suffix for in**tegrase** inhibitors: Bic**tegravir** Dolu**tegravir** Elvi**tegravir** Ral**tegravir**	Inhibit integration of viral DNA (from viral RNA) → host cell DNA by inhibiting the enzyme Integrase prevents strand transfer step of integration	Superior choice to protease inhibitors/NNRTIs → combined with two NRTIs for initial therapy → generally well tolerated → long-term viral suppression Insomnia, dizziness
Protease inhibitors	Common **-navir** suffix for protease inhibitors: **Navir** (never) **tease** a pro**tease!** Ataza**navir** Daru**navir** Indi**navir** Lopi**navir** Rito**navir** Saqui**navir** →↓ P450 → boosting agents (see class later in table)	Protease normally cleaves HIV polypeptide → reverse transcriptase, protease, integrase, other proteins; inhibiting this cleavage ↓ these proteins → viral particles cannot mature → noninfectious viral particles	Insulin resistance → hyperglycemia and hyperlipidemia; GI intolerance (nausea, diarrhea), lipodystrophy (fat redistribution → abdomen/back), hepatotoxic Indinavir → crystal-induced nephropathy, nephrolithiasis Rifampin (TB drug) ↑ P450 →↓ protease inhibitors; use rifabutin instead
Entry inhibitors	Maravir**oc** inhibits d**oc**king (see MOA) [a]Requires assay for HIV tropism (CCR5-tropic HIV vs CXCR4-tropic HIV) En**fu**virtide inhibits viral **fu**sion (see MOA)	Maravir**oc** inhibits binding of gp120 (d**oc**king protein) with CCR5 coreceptor on CD4+ macrophages and CD4+ T cells En**fu**virtide binds to gp41 → prevents **fu**sion/entry into cells	Both are infrequently used unless other drug classes fail Maraviroc: Rash, GI symptoms Enfuvirtide: Skin reaction from injections, GI symptoms
Boosting agents	Cobicistat and some protease inhibitors (rito**navir** [mainly] and saqui**navir**) inhibit CYP3A liver enzymes to increase drug levels of other treatment agents (mainly elvitegravir and protease inhibitors) and are called boosting agents They enable lower dosing, which leads to fewer adverse effects Examples: Elvitegravir-cobicistat, lopinavir-ritonavir	Boosting agents →↓ CYP3A →↑ levels of agents →↓ needed dose and ↓ adverse effects	Cobicistat →↑ serum creatine without damaging glomerular filtration rate (GFR) Rito**navir** (mainly) and saqui**navir**: See protease inhibitors' adverse effects

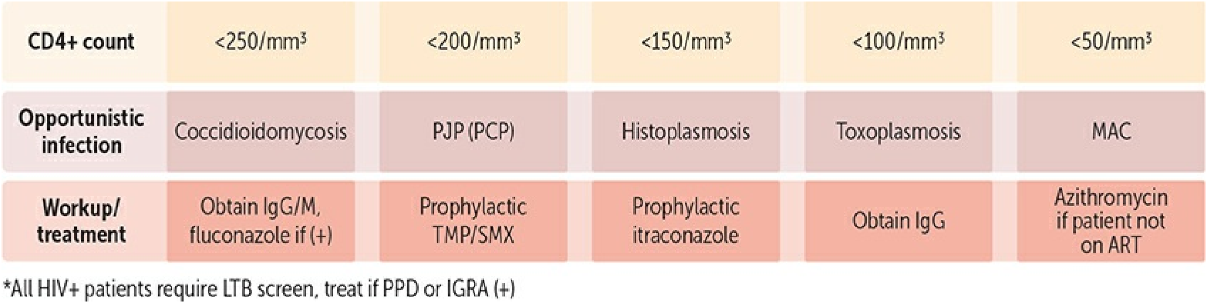
[a] Not active against HIV-2.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

Starting HIV treatment can lead to a flare-up of infectious symptoms lasting weeks to months, despite ↓ viral loads and ↑ CD4+ T cells. As the immune system becomes reconstituted (↑ CD4+ T cells) due to ART, known or unknown OIs may be present and flare up. Therefore, although treatment with HAART regimens should begin as soon as possible after HIV diagnosis, it may be delayed to first treat an OI (especially *Cryptococcus*).

PROPHYLAXIS FOR OPPORTUNISTIC INFECTIONS AND VACCINATIONS

- OIs are infections that are more common and/or more severe in advanced HIV ⊕ patients. The best prevention against OIs consists of HAART regimens that maintain CD4+ T-cell counts. Figure 2.16-11 provides a guide to prophylactic treatment against OIs.



CD4+ count	<250/mm³	<200/mm³	<150/mm³	<100/mm³	<50/mm³
Opportunistic infection	Coccidioidomycosis	PJP (PCP)	Histoplasmosis	Toxoplasmosis	MAC
Workup/ treatment	Obtain IgG/M, fluconazole if (+)	Prophylactic TMP/SMX	Prophylactic itraconazole	Obtain IgG	Azithromycin if patient not on ART

*All HIV+ patients require LTB screen, treat if PPD or IGRA (+)

FIGURE 2.16-11. Opportunistic infection prophylaxis. *MAC, Mycobacterium avium* complex; *PCP, Pneumocystis* pneumonia; *PJP, P jirovecii* pneumonia; *TMP/SMX*, trimethoprim/sulfamethoxazole. (Reproduced with permission from USMLE-Rx.com.)

- Live vaccines are contraindicated if CD4+ T-cell counts <200/mm^3. Live vaccines such as measles, mumps, and rubella (MMR); zoster; and varicella may be considered in those with less immunosuppression (higher CD4+ T-cell counts). Administration depends on the patient’s age, overall health, and other specific features.
- Other standard vaccines should be administered and include pneumococcal, meningococcal, COVID-19, hepatitis A/B, and more.

Pre-exposure prophylaxis (PrEP):

- **Indication:** High-risk HIV ⊖ patient (intravenous drug user [IVDU], MSM, sex worker, HIV ⊕ sex partner)
- **Regimen:** Tenofovir-emtricitabine taken as long as indication listed is met. PrEP is 99% and 74% effective in reducing HIV infection from sex and IV drug use, respectively. Notably, the tenofovir disoproxil fumarate/emtricitabine (TDF-FTC) formulation is more associated with kidney injury and bone loss vs the tenofovir alafenamide/emtricitabine (TAF-FTC) formulation.

Post-exposure prophylaxis:

- **Indications:**
  - **High-risk sexual contact:** Condomless sex in area with ↑ HIV prevalence with MSM and/or sex workers. Recent sexual exposure to known HIV carrier.
  - **Exposure to needles:** IV drug use with sharing of needles; healthcare worker with needlestick injury characterized by (1) exposure to potentially infective bodily fluids (blood, blood-containing fluids, bites from HIV ⊕ person, breast milk, semen, vaginal fluids) AND (2) exposure of nonintact skin and/or mucous membranes
- **Regimens:** ART ↓ likelihood of infection. A combination of three drugs is prescribed (eg, tenofovir-emtricitabine + integrase inhibitor) for 28 days. HIV testing occurs with a combination test at the start of the process and at both 6 weeks and 3 months postexposure.

Prevention of perinatal transmission:

- **Pregnant patients with HIV:** Prenatal testing for HIV is standard and uses an opt-out approach. All HIV ⊕ pregnant patients should be receiving ART. If HIV ⊕ pregnant patient is already on effective ART, the physician should continue that regimen to prevent perinatal transmission. If the patient is treatment naïve and newly diagnosed HIV ⊕, the physician should not wait for genotyping but start ART immediately. Therapies consist of two NRTIs and an integrase inhibitor or protease inhibitor.
- **At the time of delivery:**
  - If the viral RNA load <100 copies/mL and HIV ⊕ pregnant patient is on ART → vaginal delivery is recommended, and IV intrapartum zidovudine is not routinely administered.
  - If viral RNA load >1000 copies/mL → C-section is recommended, and IV intrapartum zidovudine is routinely administered.
- **Newborn therapy:**
  - If viral RNA load in the pregnant patient at the time of delivery <50 copies/mL → prescribe zidovudine to newborn for 4 to 6 weeks postbirth.
  - If viral RNA load in the pregnant patient at the time of delivery >50 copies/mL → prescribe ART with two to three drug regimens to the newborn.

KEY FACT

Pre-exposure prophylaxis with tenofovir-emtricitabine can be up to 99% effective in reducing HIV infection and should be given to high-risk patients (IVDUs, MSMs, sex workers, those with HIV-⊕ sex partners).

KEY FACT

If a patient presents with a mononucleosis-like syndrome or flulike illness with a history that places them at an increased risk for STIs, consider screening for HIV.

KEY FACT

Lifelong antiretroviral therapy should be prescribed to all HIV ⊕ patients, even during pregnancy, regardless of CD4+ T-cell count.

CYTOMEGALOVIRUS

- Seventy percent of adults in the United States have been infected with CMV, and most are asymptomatic; reactivation generally occurs in immunocompromised patients, particularly in the setting of organ transplantation.
- Transmission occurs via sexual contact, vertical transmission, breast milk, respiratory droplets in nursery or daycare facilities, and blood transfusions.
- Risk factors for reactivation include tissue or bone marrow transplant (first 100 days) and HIV/AIDS (CD4+ cell count <50/mm^3 or viral load >10,000 copies/mL).

History/PE

Systemic infection may resemble EBV mononucleosis (see the discussion on infectious mononucleosis). Specific manifestations include the following:

- **CMV retinitis:** Associated with retinal detachment (“pizza pie” retinopathy with white, fluffy, perivascular lesions). CMV retinitis presents with floaters and visual field changes (CD4+ cell count $<50/\text{mm}^3$).
- **GI and hepatobiliary involvement:** Can present with multiple nonspecific GI symptoms, including bloody diarrhea and abdominal pain. CMV, microsporidia, and *Cryptosporidium* have been implicated in the development of AIDS cholangiopathy.
- **CMV esophagitis:** Typically presents with odynophagia and shallow ulcers on the distal esophagus (CD4+ cell count $<50/\text{mm}^3$).
- **CMV pneumonitis:** Presents with cough, fever, and sparse sputum production; associated with a high mortality rate. CMV pneumonitis is much more common in patients with hematologic malignancies and transplant patients than in those with AIDS.
- **CNS involvement:** Can include polyradiculopathy, transverse myelitis, and subacute encephalitis (CD4+ cell count $<50/\text{mm}^3$; periventricular calcifications).

Diagnosis

Virus isolation, culture, histopathology (gold standard for tissue-invasive disease), serum polymerase chain reaction (PCR).

Treatment

Treat with ganciclovir, valganciclovir, or foscarnet. Treat underlying disease if the patient is immunocompromised.

CENTRAL LINE–ASSOCIATED BLOODSTREAM INFECTIONS

- Also called catheter-related bloodstream infections, central line–associated bloodstream infections (CLASBIs) are laboratory-confirmed bloodstream infections not related to an infection at a different body site that develop within 48 hours of central line placement. Catheter-related sepsis almost always occurs with central IV catheters—peripheral venous/arterial catheters are rarely implicated. Notable risk factors include emergent placement, line placement site (femoral > jugular > subclavian), type of central line (nontunneled catheter > tunneled catheter), high-risk patient factors (eg, immunosuppression), and prolonged use. CLASBIs are associated with the greatest cost burden of nosocomial infections (~$46,000/case). Prevention guidelines must be followed.
- **Microorganisms causing CLASBIs:** Gram ⊕ bacteria (40%–80% of cases: coagulase ⊖ *Staphylococci* [most common overall cause] > *Enterococci* > *Staphylococcus aureus*); gram ⊖ bacteria (20%–30% of cases: *Klebsiella* > *Enterobacter* > *Pseudomonas* > *Escherichia coli* > *Acinetobacter*); and fungi (11.8% of cases: *Candida* spp.)

History/PE

- **Nontunneled catheter:** Only 50% of patients have evidence of infection (erythema, purulence) at the site of placement. High clinical suspicion is needed in a patient with a nontunneled central line who develops systemic features of infection such as fever/chills (most common), altered mental status, hypotension, and fatigue.

- **Tunneled catheter**: In addition to systemic features of infection, the exit site and subcutaneous portions of the line need examination/palpation to evaluate for inflammation (discharge, pain).

Diagnosis

- **Best initial test:** Paired blood culture (one sample each from a peripheral vein and a central line) along with a CBC, serum electrolytes, and renal/liver function tests to assess for severity of infection and comorbidities.
- **Nontunneled catheter:** Requires one of the following: (1) isolation of same organism from a central line AND peripheral vein blood sample with a greater concentration of the organism in the central line culture; (2) isolation of the same organism from the catheter tip (>15 colony-forming units [CFUs]) and peripheral vein blood sample; and (3) shorter time to positive culture (>2 hours earlier) in central line vs peripheral vein sample.
- **Tunneled catheter:** Diagnosis requiring inflammation beyond 2 cm from the exit site, typically with pain and tenderness along the subcutaneous tract of the line, with the presence of exudate that becomes culture ⊕.

Management

- **Antibiotic therapy:** Empiric therapy should be immediately started. Do NOT wait for cultures if doing so delays antibiotic administration. With the majority of infections caused by gram ⊕/⊖ organisms, coverage is needed for both, taking into account local susceptibility patterns (eg, methicillin-resistant *S aureus* [MRSA] coverage), *Pseudomonas* coverage, and possibly fungal coverage (depending on patient characteristics). Once culture results are available, tailor therapy.
- **Catheter removal/salvage:** Nontunneled catheters should be promptly removed (limited salvage scenarios). Nontunneled lines can only be salvaged in uncomplicated (eg, no endocarditis/metastatic infection) exit site infections with topical/systemic antibiotic therapy. All tunneled catheter infections require catheter removal.

THERMAL DYSREGULATION

HYPOTHERMIA

Body temperature <35°C (<95°F) defines hypothermia. Shivering usually begins at <35°C (<95°F). Patients stop shivering at <32°C (89.6°F) and develop confusion, lethargy, and possibly cardiac arrhythmias. Patients with a body temperature <28°C (82.4°F) are usually comatose.

Etiology

- **Heat loss:** Cold environment (most common), burns, trauma
- **Impaired heat production:** Hypothyroidism, adrenal insufficiency, hypoglycemia
- **Impaired regulation:** Spinal cord injury, cerebrovascular accident

Management

Directed at correcting body temperature regardless of etiology.

Remove the patient from the cold or windy environment and remove wet clothing. Direct warming method on severity of hypothermia:

- **32° to 35°C:** Passive external rewarming. Remove wet clothing and cover with blankets or other insulation.
- **28° to 32°C:** Active external rewarming. Use warm blankets, warm water bath, or forced warm air-blanket system.
- <**28°C:** Active internal rewarming. Use warm IV fluids, warm peritoneal/pleural lavage, or extracorporeal rewarming such as hemodialysis or extracorporeal membrane oxygenation (ECMO).

Use a warm water bath to thaw frostbite. Patients will need narcotic analgesia for thawing.

Monitor the ECG for arrhythmias such as bradycardia and slow atrial fibrillation, which can be common at <30°C (86°F). The classic sign is the J wave (Osborn wave): a positive elevation at the J point, just at the end of the QRS complex.

Monitor and aggressively replace fluids. Monitor electrolytes and acid-base balance.

Do not stop resuscitation efforts until the patient has been warmed.

KEY FACT

A patient is not dead until they are warm and dead. The physician cannot pronounce death until the body is rewarmed to 32°C, unless serum K^+ is ≥12 mEq/L.

HYPERTHERMIA

Body temperature >40°C (104°F) defines hyperthermia.

Etiology

- **Exposure:** Malignant hyperthermia, neuroleptic malignant syndrome (NMS), poisoning, overdose, withdrawal syndrome, environmental (heat, classically an athlete or military recruit)
- **Infectious:** Sepsis, meningitis/encephalitis, tetanus, typhoid, malaria
- **Endocrine:** Thyroid storm, pheochromocytoma, diabetic ketoacidosis
- **Neurologic:** Hypothalamic stroke, seizures, cerebrovascular accident

Management

Directed at correcting body temperature, regardless of etiology. Rapidly cool the patient with cold water, wet blankets, and ice. Give benzodiazepines to prevent shivering, which increases metabolic demand and heat generation. Rule out causes of fever such as infection or drug reaction.

KEY FACT

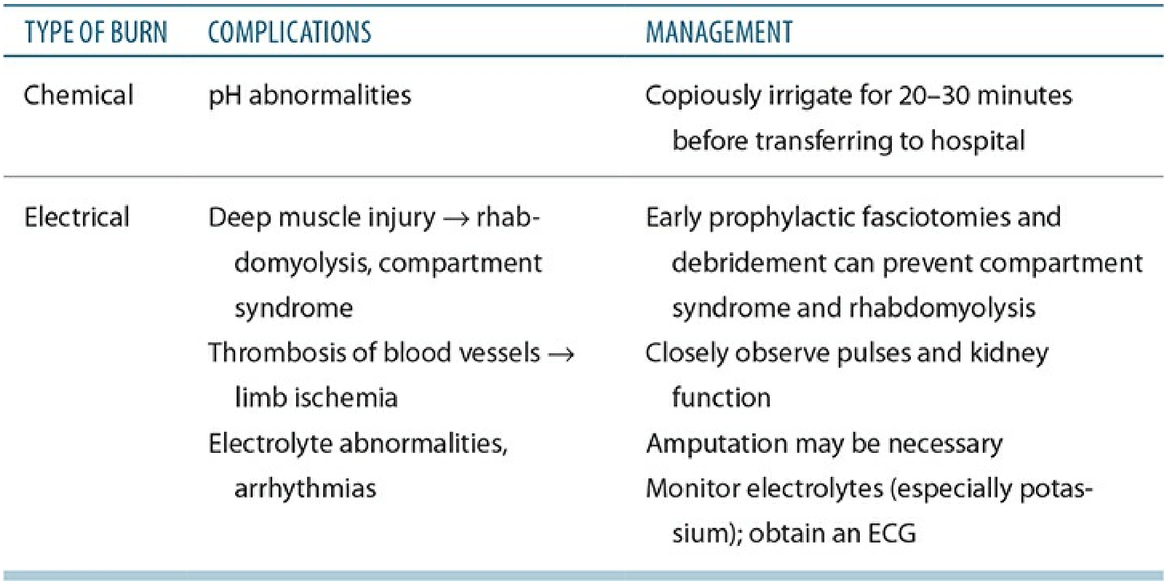
Classic causes of medication-induced hyperthermia include malignant hyperthermia, neuroleptic malignant syndrome (NMS), and serotonin syndrome (SS). Malignant hyperthermia is caused by anesthetic agents used in the OR; treat with dantrolene. NMS and SS are both caused by psychiatric medication and/or substances that have similar neuroreceptor activity.

ENVIRONMENT

BURNS

A leading cause of death in children. Patients with serious burns should be treated in an ICU setting. Burns can be chemical, electrical, or thermal. Chemical and electrical burns require special considerations found in Table 2.16-6. Burns of all types are categorized by depth of tissue destruction (see Fig. 2.16-12):

TABLE 2.16-6. **Special Considerations in Chemical and Electrical Burns**



TYPE OF BURN	COMPLICATIONS	MANAGEMENT
Chemical	pH abnormalities	Copiously irrigate for 20–30 minutes before transferring to hospital
Electrical	Deep muscle injury → rhabdomyolysis, compartment syndrome	Early prophylactic fasciotomies and debridement can prevent compartment syndrome and rhabdomyolysis
	Thrombosis of blood vessels → limb ischemia	Closely observe pulses and kidney function
	Electrolyte abnormalities, arrhythmias	Amputation may be necessary
		Monitor electrolytes (especially potassium); obtain an ECG

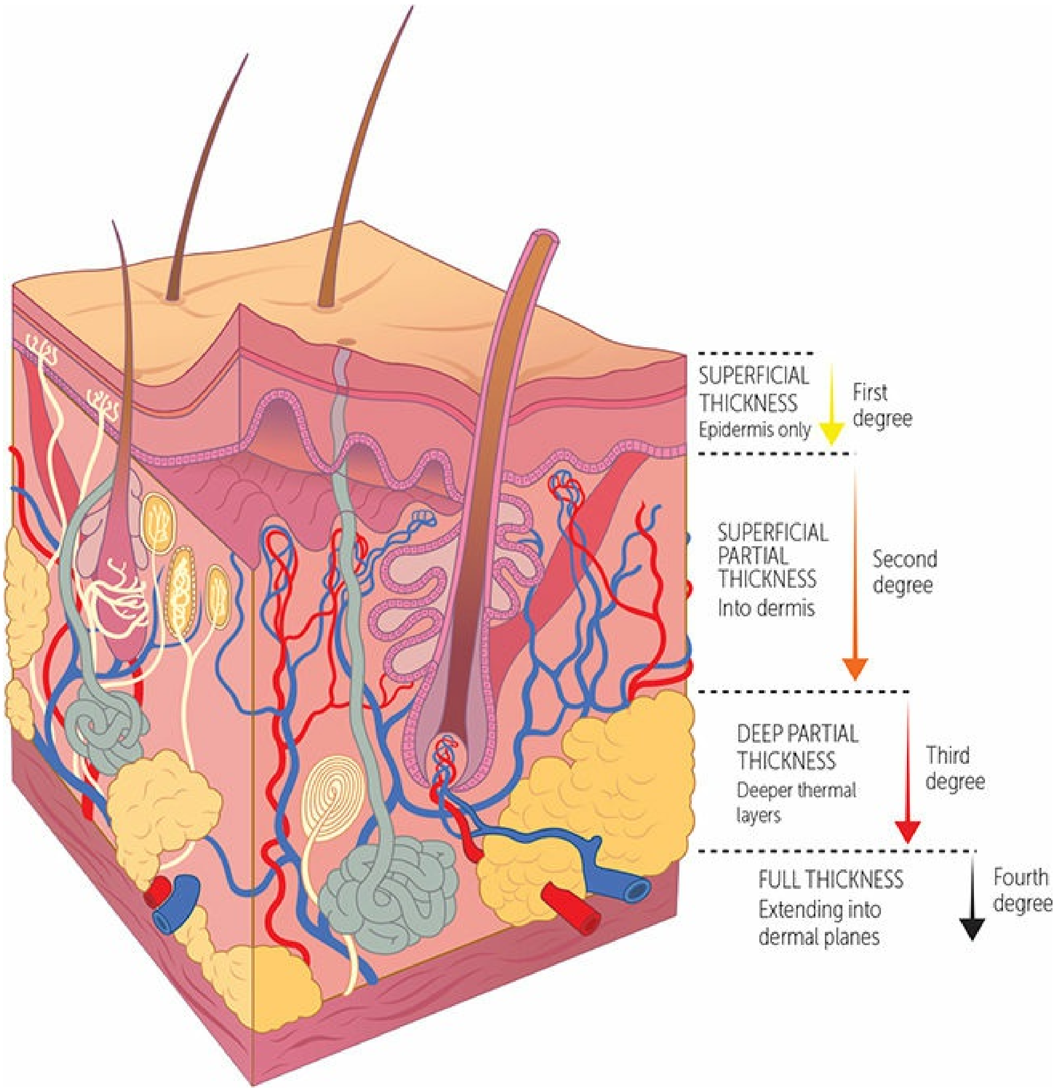

SUPERFICIAL THICKNESS
Epidermis only
First degree
SUPERFICIAL PARTIAL THICKNESS
Into dermis
Second degree
DEEP PARTIAL THICKNESS
Deeper thermal layers
Third degree
FULL THICKNESS
Extending into dermal planes
Fourth degree

FIGURE 2.16-12. **Depth of burn wounds.** (Reproduced with permission from USMLE-Rx.com.)

- **Superficial thickness/first degree:** Only the epidermis is involved. The area is painful and erythematous without blisters. Capillary refill is intact.
- **Partial thickness/second degree:** The epidermis and partial thickness of the dermis are involved. The area is painful and blistered.
- **Full thickness/third degree:** The epidermis and the full thickness of the dermis are involved. The area is painless, white, charred, and without capillary refill.
- **Fourth degree:** The thermal injury involves the epidermis; full dermis; and underlying bone, muscle, and/or fascia.

KEY FACT

Superinfection in burns is commonly caused by *Pseudomonas* or gram ⊕ cocci.

History/PE

- Patients may present with obvious skin wounds, but significant deep destruction may not be visible, especially with electrical burns.
- Determine whether inhalation of smoke occurred, as it would in a closed-space fire (risk

for carbon monoxide [CO] poisoning) or with burning carpets and textiles (risk for cyanide poisoning).

- Conduct a thorough airway and lung examination to assess for inhalation injury.

Diagnosis

- **Best initial step:** Assess ABCs. If evidence of thermal or inhalation injury to the upper airway exists, intubate.
- **Next step:** Evaluate the percentage of body surface area (% BSA) involved (see Fig. 2.16-13).

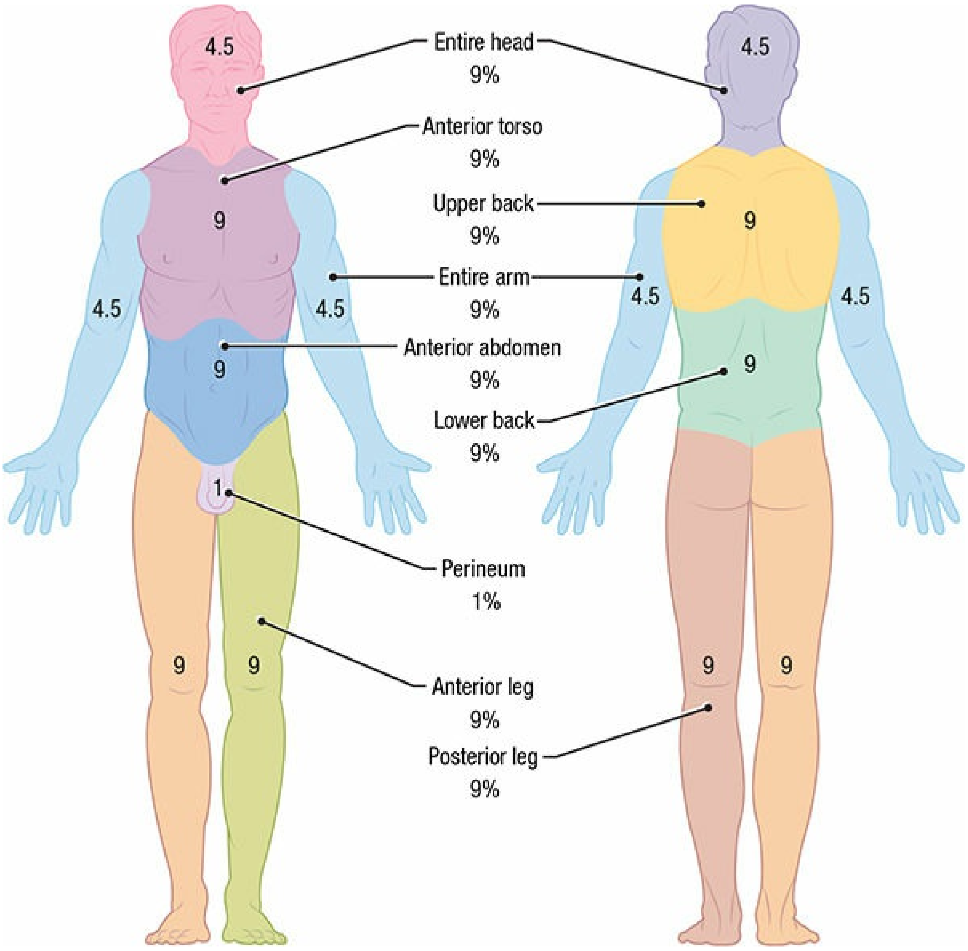

4.5
Entire head
9%
4.5
Anterior torso
9%
Upper back
9%
9
9
Entire arm
9%
4.5
4.5
4.5
4.5
Anterior abdomen
9%
9
9
Lower back
9%
1
Perineum
1%
9
9
9
9
Anterior leg
9%
Posterior leg
9%

FIGURE 2.16-13. **The rule of 9s in the estimation of BSA.** Estimation of BSA is imperative in the evaluation of burn victims. (Reproduced with permission USMLE-Rx.com.)

- In patients exposed to smoke, suspect inhalation injury, CO poisoning, and cyanide poisoning. Obtain a CXR, carboxyhemoglobin level, and lactate.
- Assess for circumferential eschar formation, which can obstruct venous and lymphatic drainage, leading to vascular compromise and compartment syndrome.

Treatment

- **Best initial treatment:** Fluid repletion. For second- and third-degree burns, initiate fluids based on the Parkland formula. Titrate fluids to maintain at least 1 cc/kg/hr urine output.

KEY FACT

Parkland formula: Fluids for the first 24 hours (in mL) = 4 × patient's weight in kg × % BSA. Give 50% of fluids over the first 8 hours from the time of injury and the remaining 50% over the following 16 hours.

- Topical antimicrobials (eg, mafenide acetate or silver sulfadiazine) can be used prophylactically when the epidermis is no longer intact. There is no proven benefit associated with the use of PO/IV antibiotics or corticosteroids.
- Perform an escharotomy to relieve obstructed vascular flow in circumferential burns.
- Other management includes tetanus vaccination, if appropriate; stress ulcer prophylaxis; and IV narcotic analgesia.

DROWNING

Assess for hypotension, hypothermia, and hypoxemia. May have cervical spine injuries, so cervical spine should be immobilized until this is ruled out.

Diagnosis

Diagnostic testing:

- Primary and secondary survey
- Chest radiography
- CBC and arterial blood gas

Treatment

- Remove wet clothes and rewarm
- Correct hypoxemia and acidosis

HIGH-ALTITUDE SICKNESS

Typically hours after a fast ascent with higher risk at extreme altitude (>20,000 feet).

Diagnosis

Clinical diagnosis.

- Acute mountain sickness: dizziness, headache, fatigue, nausea, vomiting
- High-altitude pulmonary edema: cough, shortness of breath, hypoxia, crackles on auscultation
- High-altitude cerebral edema: severe fatigue, confusion, ataxia

Treatment

- Supplemental O_2
- Nonsteroidal anti-inflammatory drugs (NSAIDs) for treating headaches
- Acetazolamide
- Dexamethasone
- Descent from high altitude

KEY FACT

Common microbiology of bites: *Pasteurella* species, *Capnocytophaga canimorsus*, *Bartonella*, and *Staphylococcus* and *Streptococcus* species.

KEY FACT

Bites involving sharp teeth and resulting in deep puncture should not be sutured closed. Treat with amoxicillin/clavulanic acid and monitor for developing deep tissue infections, including osteomyelitis.

BITES AND STINGS

Figures 2.16-14 and 2.16-15 summarize the recommended prophylaxis for rabies and tetanus. Table 2.16-7 outlines the management of common bites and stings.

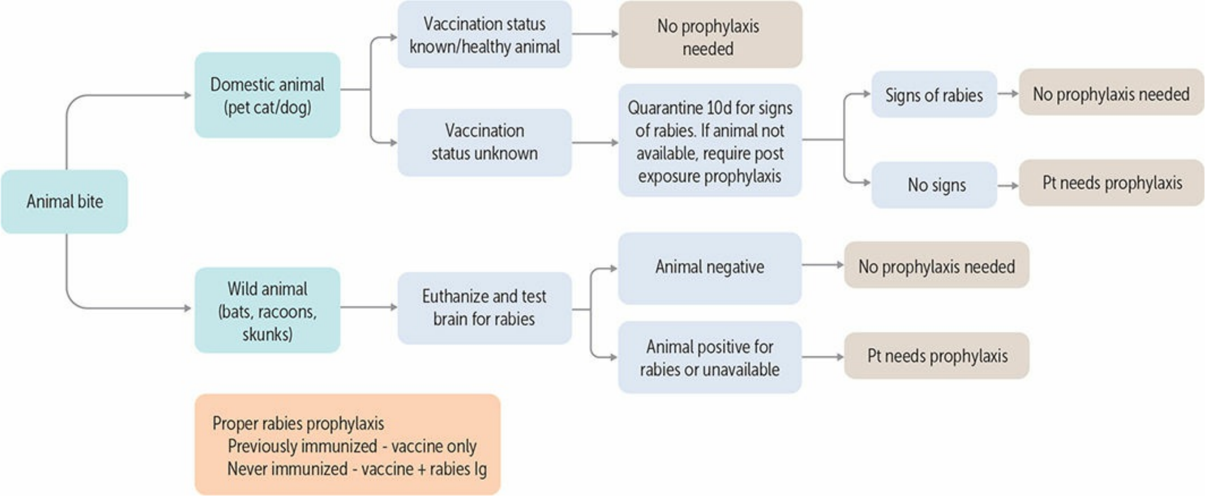

Animal bite
Domestic animal (pet cat/dog)
Vaccination status known/healthy animal
No prophylaxis needed
Vaccination status unknown
Quarantine 10d for signs of rabies. If animal not available, require post exposure prophylaxis
Signs of rabies
No prophylaxis needed
No signs
Pt needs prophylaxis
Wild animal (bats, racoons, skunks)
Euthanize and test brain for rabies
Animal negative
No prophylaxis needed
Animal positive for rabies or unavailable
Pt needs prophylaxis
Proper rabies prophylaxis
Previously immunized - vaccine only
Never immunized - vaccine + rabies Ig

FIGURE 2.16-14. Rabies postexposure prophylaxis algorithm. (Reproduced with permission from USMLE-Rx.com.)

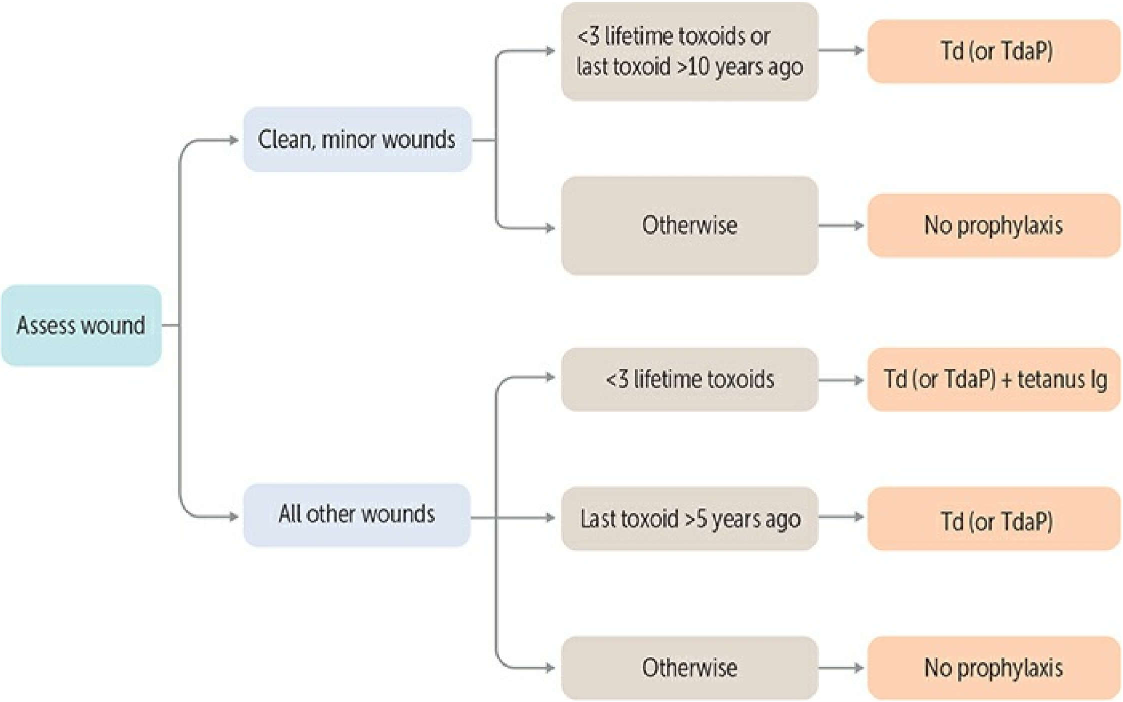

Assess wound
Clean, minor wounds
<3 lifetime toxoids or last toxoid >10 years ago
Td (or TdaP)
Otherwise
No prophylaxis
All other wounds
<3 lifetime toxoids
Td (or TdaP) + tetanus Ig
Last toxoid >5 years ago
Td (or TdaP)
Otherwise
No prophylaxis

FIGURE 2.16-15. **Tetanus prophylaxis algorithm.** (Reproduced with permission from USMLE-Rx.com.)

TABLE 2.16-7. **Management of Bites and Stings**

SOURCE	POTENTIAL COMPLICATION	MANAGEMENT
Bees and wasps	Anaphylaxis	Antihistamines and steroids; intramuscular (IM) epinephrine if anaphylaxis develops
Spiders	Black widow: Muscular spasms (can mimic rigid acute abdomen but no rebound) Brown recluse: Necrosis, flulike symptoms, disseminated intravascular coagulation	Black widow: Antivenin; classic treatment with Ca^{2+} gluconate is largely proven ineffective Brown recluse: Cold compresses slow necrosis; dapsone may help (contraindicated in G6PD deficiency); debridement should be limited to obviously necrotic tissue

SOURCE	POTENTIAL COMPLICATION	MANAGEMENT
Scorpions	In severe cases, neuromuscular toxicity manifests as cranial nerve dysfunction, excessive motor activity (can be mistaken for seizure), autonomic dysfunction (hypersalivation), and/or respiratory compromise	Antivenin if neuromuscular symptoms develop; if no antivenin is administered, benzodiazepines and analgesics help pain and spasms
Snakes (Crotaline species: rattlesnake, copperhead)	Local necrosis, distributive shock, disseminated intravascular coagulation	Antivenin (Crotalidae polyvalent immune Fab) is the mainstay of treatment; keep the affected limb below the heart Compression bands, tourniquets, prophylactic fasciotomy, and resection are ineffective or outdated treatments and probably the wrong answer
Dogs and cats	Infection, rabies/tetanus	Amoxicillin/clavulanate for puncture wounds, bites to hands/feet, and high-risk or immunocompromised patients The physician should consider imaging cat bites for possible tooth fragments implanted in wound
Humans	Infection	Amoxicillin/clavulanate
Rodents	Low risk for infection; not known to carry rabies Contact with wild rodents is a risk factor for leptospirosis	Local wound care only
Shellfish (*Vibrio vulnificus)*	Severe necrotizing fasciitis and hemorrhagic bullous lesions Patients with preexisting liver disease (especially hemochromatosis) have an increased risk	IV doxycycline and ceftriaxone, emergent surgical debridement

TOXICOLOGY

RESUSCITATION OF THE POISONED PATIENT

Evaluation

- Consider and evaluate for toxic ingestion in any patient presenting with altered mental status or unexplained seizure-like activity.
- Airway, breathing, and circulation always take precedence in the resuscitation of the potentially poisoned patient.
- ECG changes and cardiac dysrhythmias are common in overdose. An initial ECG should be obtained in the evaluation of the poisoned patient.
- A thorough neurologic examination, including pupil reactivity, muscle tone, and reflexes, is important to note and can help differentiate toxidromes that otherwise present very similarly.

Decontamination

As part of the resuscitation of a poisoned patient, decontamination should be considered. The main goal of decontamination is preventing further drug absorption. Recent ingestions (<2 hours) should generally receive activated charcoal (exceptions are lithium, iron, lead, hydrocarbons, or toxic alcohols). Care should be taken with lethargic patients because aspiration of activated charcoal can cause pneumonitis. Orogastric lavage is rarely indicated but may help for lethal toxins ingested <1 hour prior. Ipecac syrup is an antiquated treatment for poisoning that is never used because of the risk for ↑ damage caused by emesis and the lack of demonstrated benefit.

HIGH-YIELD TOXICITIES

Carbon Monoxide Poisoning

A hypoxemic poisoning syndrome seen in patients who have been exposed to automobile exhaust, smoke inhalation, barbecues, or old appliances in poorly ventilated locations.

History/PE

- Presents with headaches and confusion. Cherry-red skin discoloration is rare. Coma or seizures occur in severe cases.
- Chronic low-level exposure may cause flulike symptoms with generalized myalgias, nausea, and headaches. The physician should ask about symptoms in others living in the same place.
- The physician should suspect smoke inhalation in the presence of singed nose hairs, facial burns, hoarseness, wheezing, or carbonaceous sputum.

Diagnosis

- Assessment of serum carboxyhemoglobin level, using co-oximetry (normal is <5% in nonsmokers and <10% in smokers).
- The physician should perform an ECG in older adult patients and those with a history of cardiac disease to evaluate for evidence of cardiac ischemia.
- A pregnancy test should be checked in women of childbearing age.

Treatment

- The physician should treat with 100% O_2 facemask until the patient is asymptomatic and the carboxyhemoglobin level on co-oximetry falls to normal.
- Indications for hyperbaric O_2: Pregnancy (↑ affinity of CO to fetal hemoglobin [Hb]), signs of CNS or cardiac ischemia, or severely ↑ carboxyhemoglobin (>25%).
- Intubate early in patients with airway burns or smoke inhalation, as upper airway edema can rapidly lead to complete obstruction.

KEY FACT

In carbon monoxide poisoning, the measured O_2 saturation is usually normal. This is because the pulse oximeter recognizes carboxyhemoglobin as a normal saturated hemoglobin molecule, so it does not adequately reflect the low arterial PO_2 levels.

Methemoglobinemia

A syndrome of hypoxemia after exposure to an oxidizing agent (eg, local anesthetics, dapsone, nitrites) that oxidizes ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}), resulting in impaired oxygen transportation.

KEY FACT

Induced methemoglobinemia using nitrites is a treatment strategy for cyanide toxicity because oxidized hemoglobin binds with high affinity to cyanide, competing with cyanide's binding to cytochrome C.

History/PE

History of exposure to local anesthetic, nitrite, or dapsone. Cyanosis with "chocolate-colored blood" on blood draw.

Q

A 36-year-old woman is brought in by emergency medical services after suspected cocaine overdose. The patient is found to be in ventricular tachycardia and, after cardioversion, complains of abdominal pain. What study should be ordered?

Diagnosis

- The physician should not rely on pulse oximetry and partial pressure of oxygen (PO_2). Pulse oximetry will be low, and PO_2 will be falsely normal.
- Direct methemoglobin measurement using co-oximetry can confirm diagnosis.

Treatment

- Methylene blue
- Table 2.16-8 summarizes antidotes and treatments for substances commonly encountered in overdoses and poisonings

TABLE 2.16-8. Antidotes and Management of Other Toxic Ingestions/Overdoses

TOXIN	ANTIDOTE/TREATMENT	NOTES
Acetaminophen	In acute overdose: *N*-acetylcysteine (NAC), repletes glutathione In chronic overdose, supportive care	Charcoal is useful if patient presents within 4 hours of overdose along with NAC Always administer NAC in acute overdose >7.5 g ingested; otherwise, get acetaminophen level and treat if level >150 at 4 hours
Acid/alkali ingestion	Assess ABCs, and remove affected clothing Upper endoscopy 6–24 hours after endoscopy Do not try to neutralize acid or base, and do not induce vomiting Activated charcoal is CONTRAINDICATED in acid/alkali ingestions	Timing of endoscopy is critical, as early endoscopy may fail to characterize the extent of the damage, and late endoscopy is associated with perforation Neutralization generates copious amounts of heat, and vomiting worsens esophageal injury If the eyes are involved, the eyes should be irrigated with copious amounts of water for at least 15 minutes before traveling to the emergency department
Anticholinesterases, organophosphates	Atropine, pralidoxime (reactivates acetylcholinesterase)	Found in insecticides and sarin nerve gas
Antimuscarinic/anticholinergic agents	Physostigmine	Most common source is antihistamine medications with anticholinergic adverse effects
Arsenic, mercury	Succimer, dimercaprol	Arsenic poisoning from contaminated industrial areas or landfills; acute toxicity is associated with garlic breath and GI symptoms; chronic toxicity is associated with skin discoloration and peripheral neuropathy Mercury poisoning from thermometers and old paints

TOXIN	ANTIDOTE/TREATMENT	NOTES
β-blockers	Glucagon	Glucagon is a positive inotrope and increases heart rate via a mechanism that bypasses the adrenergic β-receptors
Barbiturates (phenobarbital)	Urine alkalinization, dialysis, activated charcoal, supportive care	No direct antidote is available
Benzodiazepines	Supportive care (intubation if necessary), flumazenil	Never use flumazenil in the setting of chronic benzodiazepine use, even if patient is acutely intoxicated; it can produce deadly withdrawal seizures
Copper, arsenic, lead, gold	Penicillamine	Penicillamine is a chelating agent that sequesters heavy metals
Cyanide	Hydroxocobalamin, amyl nitrate, sodium nitrite, sodium thiosulfate	Nitrites induce methemoglobinemia, which binds cyanate
Digitalis	Digoxin immune Fab (fragment antigen binding antibodies in symptomatic patients; arrhythmia, altered mental status, acute kidney injury, hyperkalemia)	Do not treat hyperkalemia or hypocalcemia before giving antidote because these conditions often correct themselves once the Na^+/K^+ pump is working
Heparin	Protamine sulfate	Protamine-heparin antibodies may induce a clinical syndrome similar to HITT
Iron	Deferoxamine	Look for radiopaque tablets on x-ray in a child with hematemesis and metabolic acidosis
Lead	Succimer, ethylenediaminetetraacetic acid, dimercaprol	Sources of lead include old paint, soil, toys, jewelry, and drinking water
Methanol Ethylene glycol (antifreeze)	Fomepizole is the treatment of choice; ethanol can be used if fomepizole is contraindicated or unavailable	Poisoning from methanol and ethylene glycol results from the active metabolites, which are produced by a reaction mediated by alcohol dehydrogenase; fomepizole and ethanol inhibit the reaction that forms the toxic metabolite
Opioids	Naloxone	It is common to empirically treat patients found unconscious with naloxone
Salicylates	Urine alkalinization, dialysis, activated charcoal	Symptoms of poisoning include nausea, vomiting, and tinnitus
Tricyclic antidepressants	Sodium bicarbonate, diazepam, or lorazepam for seizures/agitation	Monitor closely and only give sodium bicarbonate if QRS >100 msec or ventricular arrhythmia is present
Tissue plasminogen activator, streptokinase	Aminocaproic acid	Overdose may result in hemorrhage and/or angioedema
Warfarin	Fresh frozen plasma (immediate reversal in hemorrhaging patient), vitamin K (long-term reversal)	Warfarin overdose may occur if a patient is concomitantly taking CYP450 inhibitors

KEY FACT

Serum cyanide concentration is a slow lab test that will not result in time to save the patient. Diagnose cyanide poisoning based on high clinical suspicion (inhalation of burning carpet/textiles and elevated lactate).

A

Cocaine use may lead to nonobstructive mesenteric ischemia because of perfusion deficits secondary to cardiac arrhythmias. Abdominal CT angiography should be ordered to screen for ischemia in those with abdominal pain.

COMMON DRUG INTERACTIONS AND REACTIONS

Drug-drug interactions and adverse effects are a common cause of toxicity in patients. Table 2.16-9 outlines drug interactions and reactions that are commonly encountered.

TABLE 2.16-9. **Drug Interactions and Reactions**

INTERACTION/REACTION	DRUGS
Induction of P450 enzymes	**Barb**iturates, **St**. John's wort, **P**henytoin, **R**ifampin, **G**riseofulvin, **C**arbamazepine (**Barb**ara **St**eals **P**hen-phen and **R**efuses **G**reasy **C**arbs)
Inhibition of P450 enzymes	Quinidine, cimetidine, ketoconazole, isoniazid (isonicotinic acid hydrazide [INH]), grapefruit, erythromycin, sulfonamides
Metabolism by P450 enzymes	Sedatives: Benzodiazepines, barbiturates Cardiac drugs: Metoprolol, propranolol, nifedipine, warfarin, quinidine Anticonvulsants: Phenytoin, carbamazepine Other: Theophylline, amide anesthetics
Risk for digoxin toxicity	Quinidine, cimetidine, amiodarone, calcium channel blockers (CCBs)
Competition for albumin-binding sites	Warfarin, ASA, phenytoin
Blood dyscrasias	Ibuprofen, quinidine, methyldopa, chemotherapeutic agents
Hemolysis in G6PD-deficient patients	Sulfonamides, INH, acetylsalicylic acid (ASA), ibuprofen, nitrofurantoin, primaquine, pyrimethamine, chloramphenicol, dapsone
Gynecomastia	**S**pironolactone, **D**igitalis, **C**imetidine, chronic **A**lcohol use, **K**etoconazole (**S**ome **D**rugs **C**reate **A**wesome **K**nowledge)
Stevens-Johnson syndrome	Lamotrigine, sulfonamides, penicillins
Photosensitivity	Tetracycline, amiodarone, sulfonamides
Drug-induced SLE	Procainamide, hydralazine, INH, penicillamine, chlorpromazine, methyldopa, quinidine

MAJOR DRUG ADVERSE EFFECTS

Table 2.16-10 outlines the major adverse effects of select drugs.

TABLE 2.16-10. **Drug Adverse Effects**

DRUG	ADVERSE EFFECTS
Angiotensin-converting enzyme inhibitors	Cough, rash, proteinuria, angioedema, taste changes, teratogenesis (renal agenesis)
Acyclovir	Crystalluria → acute tubular necrosis (ATN) 2/2 renal tubular obstruction (administer IV fluids with drug to lower risk for AKI)
Amantadine	Ataxia, livedo reticularis, anticholinergic adverse effects (dry mouth, urinary retention, constipation)
Aminoglycosides (especially amikacin)	Ototoxicity, nephrotoxicity (acute tubular necrosis), neuromuscular blockade
Amiodarone	Acute: Atrioventricular (AV) block, hypotension, bradycardia Chronic: Pulmonary fibrosis, peripheral deposition leading to bluish discoloration, arrhythmias, hypo-/hyper-thyroidism, corneal deposition, hepatotoxicity
Amphotericin	Fever/rigors, nephrotoxicity, bone marrow suppression, anemia
Antihistamines (first generation)	Potent anticholinergic effects (eye and oropharyngeal dryness, urinary retention)
Antipsychotics	Sedation, acute dystonic reaction, akathisia, parkinsonism, tardive dyskinesia, NMS, QT prolongation
Azoles (eg, fluconazole)	Inhibition of P450 enzymes
Azathioprine	Diarrhea, leukopenia, hepatotoxicity
β-blockers	Asthma exacerbation, masking of hypoglycemia, impotence, bradycardia, AV block, CHF
Benzodiazepines	Sedation, dependence, respiratory depression
Bile acid resins	GI upset, malabsorption of vitamins and medications
Carbamazepine	Autoinduction of P450 enzymes (induces P450 enzymes that break down carbamazepine—requires dose increase 2–3 weeks after initiation), agranulocytosis/aplastic anemia, liver toxicity, Steven-Johnson syndrome
CCBs	Peripheral edema, constipation, cardiac depression
Chloramphenicol	Gray baby syndrome, aplastic anemia
Cisplatin	Nephrotoxicity, neurotoxicity (eg, peripheral neuropathy, acoustic nerve damage)
Clonidine	Dry mouth; severe rebound headache and hypertension
Clozapine	Agranulocytosis
Corticosteroids	Depression and other psychological conditions, hyperglycemia (acute), immunosuppression, bone mineral loss, osteonecrosis, thinning of skin, easy bruising, myopathy, cataracts (chronic)
Cyclophosphamide	Myelosuppression, hemorrhagic cystitis, bladder cancer

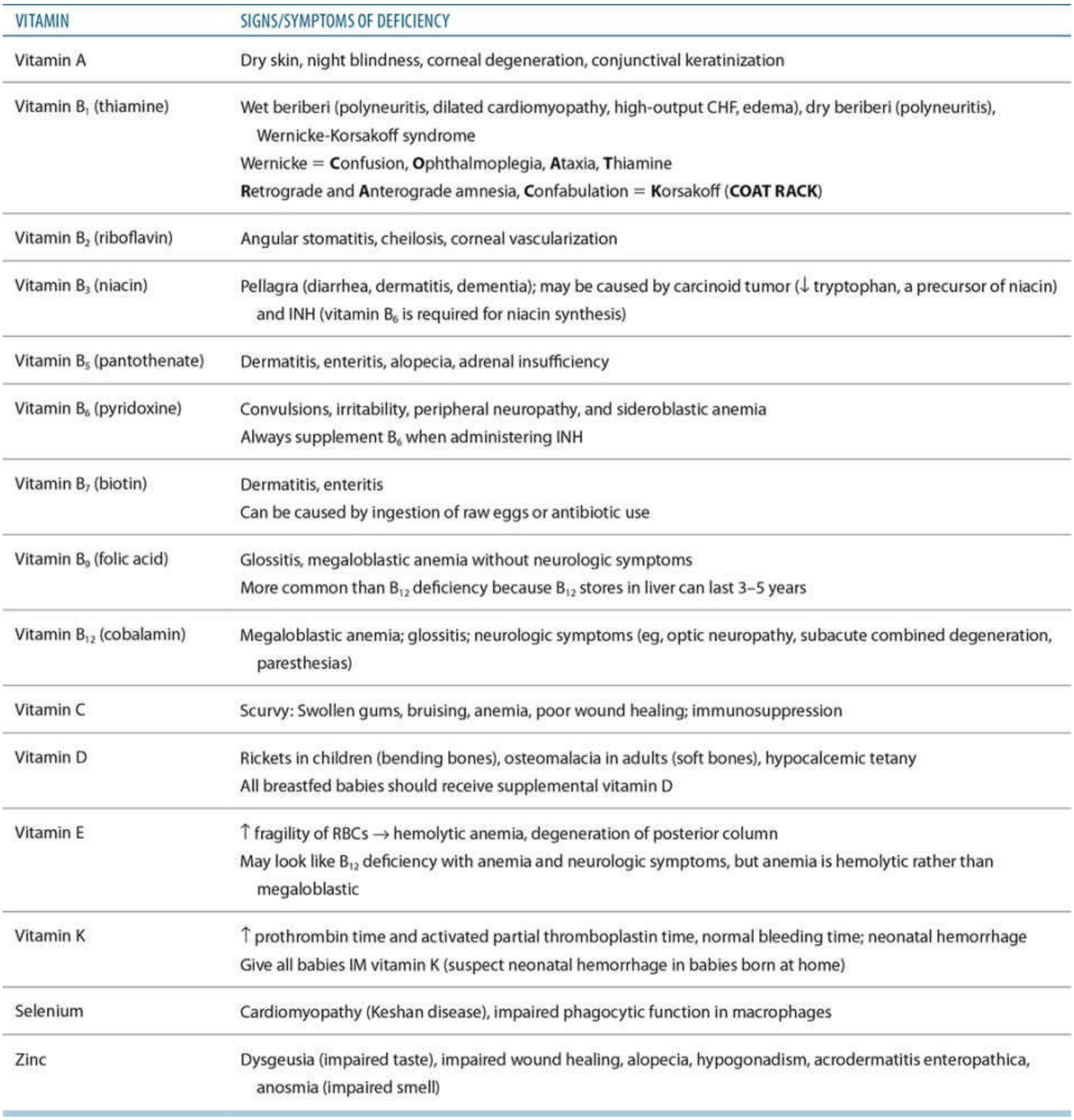
Digoxin	GI disturbance, yellow visual changes, arrhythmias (eg, junctional or supraventricular tachycardia)
Diphenhydramine	Anticholinergic (tachycardia, hyperthermia, mydriasis, reduced bowel sounds) and antihistaminic (drowsiness, confusion)
Doxorubicin	Cardiotoxicity (cardiomyopathy), urine discoloration
Fluoroquinolones	Cartilage damage in children; Achilles tendon rupture in adults
Furosemide	Ototoxicity, hypokalemia, nephritis, gout
Gemfibrozil	Myositis, reversible ↑ in LFTs
Halothane	Hepatotoxicity, malignant hyperthermia
Hydrochlorothiazide	Hypokalemia, hyponatremia, hyperuricemia, hyperglycemia, hypercalcemia, sulfa allergy
HMG-CoA reductase inhibitors (statins)	Myositis, reversible ↑ in LFTs
Hydralazine	Drug-induced SLE
Hydroxychloroquine	Retinopathy (requires annual ophthalmologic exam for long-term use)
INH	Peripheral neuropathy (prevent with pyridoxine/vitamin B_6), hepatotoxicity, inhibition of P450 enzymes, seizures with overdose, hemolysis in G6PD deficiency
Monoamine oxidase inhibitors	Hypertensive tyramine reaction, serotonin syndrome (with other serotonergic agents)
Metformin	Lactic acidosis (acute kidney injury, dehydration, sepsis), vitamin B_{12} deficiency; withhold metformin until condition improves
Methotrexate	Hepatic fibrosis, pneumonitis, anemia
Metoclopramide	Extrapyramidal symptoms: Acute dystonia, akathisia, parkinsonism
Methyldopa	⊕ Coombs test, drug-induced SLE
Metronidazole	Disulfiram reaction, vestibular dysfunction, metallic taste
Mycophenolate mofetil	Bone marrow suppression
Niacin	Cutaneous flushing
Nitroglycerin	Hypotension, tachycardia, headache, tolerance
Penicillamine	Drug-induced SLE
Penicillin/β-lactams	Hypersensitivity reactions
Phenytoin	Nystagmus, diplopia, ataxia, arrhythmia (in toxic doses), gingival hyperplasia, hirsutism, teratogenic effects
Prazosin	First-dose hypotension, priapism

Procainamide	Drug-induced SLE
Propylthiouracil	Agranulocytosis, aplastic anemia
Quinidine	Cinchonism (headache, tinnitus), thrombocytopenia, arrhythmias (eg, torsades de pointes)
Reserpine	Depression, drug-induced parkinsonism
Rifampin	Induction of P450 enzymes; orange-red body secretions
Salicylates	Fever; hyperventilation with respiratory alkalosis and metabolic acidosis; dehydration, diaphoresis, hemorrhagic gastritis
SSRIs	Anxiety, sexual dysfunction, serotonin syndrome if taken with other serotonergic agents or with recent dose escalation
Succinylcholine	Malignant hyperthermia, hyperkalemia
TCAs	Coma, anticholinergic effects, seizures, QRS prolongation, arrhythmias
Tetracyclines	Tooth discoloration, photosensitivity, Fanconi syndrome, GI distress
Trazadone	Priapism ("Traza**done** = Traza**BONE**"), QT prolongation, serotonin syndrome
Trimethoprim	Megaloblastic anemia, leukopenia, granulocytopenia, hyperkalemia
Valproic acid	Teratogenicity leads to neural tube defects; rare fatal hepatotoxicity
Vancomycin	Nephrotoxicity, ototoxicity, "red man syndrome" (histamine release; not an allergy)
Vinblastine	Severe myelosuppression
Vincristine	Peripheral neuropathy, paralytic ileus
Zidovudine	Thrombocytopenia, megaloblastic anemia

VITAMIN DEFICIENCIES

Table 2.16-11 summarizes the signs and symptoms of key vitamin deficiencies.

TABLE 2.16-11. Vitamin Deficiencies



VITAMIN	SIGNS/SYMPTOMS OF DEFICIENCY
Vitamin A	Dry skin, night blindness, corneal degeneration, conjunctival keratinization
Vitamin B_1 (thiamine)	Wet beriberi (polyneuritis, dilated cardiomyopathy, high-output CHF, edema), dry beriberi (polyneuritis), Wernicke-Korsakoff syndrome Wernicke = **C**onfusion, **O**phthalmoplegia, **A**taxia, **T**hiamine **R**etrograde and **A**nterograde amnesia, **C**onfabulation = **K**orsakoff (**COAT RACK**)
Vitamin B_2 (riboflavin)	Angular stomatitis, cheilosis, corneal vascularization
Vitamin B_3 (niacin)	Pellagra (diarrhea, dermatitis, dementia); may be caused by carcinoid tumor (↓ tryptophan, a precursor of niacin) and INH (vitamin B_6 is required for niacin synthesis)
Vitamin B_5 (pantothenate)	Dermatitis, enteritis, alopecia, adrenal insufficiency
Vitamin B_6 (pyridoxine)	Convulsions, irritability, peripheral neuropathy, and sideroblastic anemia Always supplement B_6 when administering INH
Vitamin B_7 (biotin)	Dermatitis, enteritis Can be caused by ingestion of raw eggs or antibiotic use
Vitamin B_9 (folic acid)	Glossitis, megaloblastic anemia without neurologic symptoms More common than B_{12} deficiency because B_{12} stores in liver can last 3–5 years
Vitamin B_{12} (cobalamin)	Megaloblastic anemia; glossitis; neurologic symptoms (eg, optic neuropathy, subacute combined degeneration, paresthesias)
Vitamin C	Scurvy: Swollen gums, bruising, anemia, poor wound healing; immunosuppression
Vitamin D	Rickets in children (bending bones), osteomalacia in adults (soft bones), hypocalcemic tetany All breastfed babies should receive supplemental vitamin D
Vitamin E	↑ fragility of RBCs → hemolytic anemia, degeneration of posterior column May look like B_{12} deficiency with anemia and neurologic symptoms, but anemia is hemolytic rather than megaloblastic
Vitamin K	↑ prothrombin time and activated partial thromboplastin time, normal bleeding time; neonatal hemorrhage Give all babies IM vitamin K (suspect neonatal hemorrhage in babies born at home)
Selenium	Cardiomyopathy (Keshan disease), impaired phagocytic function in macrophages
Zinc	Dysgeusia (impaired taste), impaired wound healing, alopecia, hypogonadism, acrodermatitis enteropathica, anosmia (impaired smell)

DISEASES ASSOCIATED WITH NEOPLASMS

Table 2.16-12 outlines conditions that are commonly associated with neoplasms.

TABLE 2.16-12. Disorders Associated With Neoplasms

CONDITION	NEOPLASM
Acanthosis nigricans (hyperpigmentation and epidermal thickening) and seborrheic keratoses	Visceral malignancy (eg, stomach, lung, breast, uterus)
Actinic keratosis	Squamous cell carcinoma of the skin
AIDS	Aggressive, malignant non-Hodgkin lymphomas, Kaposi sarcoma, cervical cancer
Autoimmune diseases (eg, myasthenia gravis)	Thymomas
Barrett esophagus (chronic GI reflux)	Esophageal adenocarcinoma
Chronic atrophic gastritis, pernicious anemia, postsurgical gastric remnants	Gastric adenocarcinoma
Cirrhosis (eg, alcohol use disorder, hepatitis B virus, hepatitis C virus, Wilson disease)	Hepatocellular carcinoma
Down syndrome	**ALL** ("We will **ALL** go **Down** together"), AML
Immunodeficiency states	Malignant lymphomas
Multiple dysplastic nevi	Malignant melanoma
Neurofibromatosis type 1	Pheochromocytoma, neurofibroma, optic glioma
Neurofibromatosis type 2	Acoustic schwannoma
Paget disease of bone	Secondary osteosarcoma and fibrosarcoma
Plummer-Vinson syndrome (atrophic glossitis, esophageal webs, anemia; all caused by iron deficiency)	Squamous cell carcinoma of the esophagus
Tuberous sclerosis (facial angiofibroma, seizures, intellectual disability)	Astrocytoma and cardiac rhabdomyoma
Ulcerative colitis	Colonic adenocarcinoma
Xeroderma pigmentosum	Squamous cell and basal cell carcinomas of the skin

TRAUMA MANAGEMENT

The advanced trauma life support (ATLS) algorithm divides management into two phases: the primary survey focuses on resuscitation and gross identification of injuries, whereas the secondary survey serves as a more detailed head-to-toe assessment of the patient. Many USMLE questions on trauma depend on knowing the order of the primary and secondary surveys. Remember, establishing and maintaining airway patency takes precedence over all other treatments.

KEY FACT

Remember the rhyme, "GCS 8 (or less), intubate!"

PRIMARY SURVEY

Airway

- **Assessment:** If the patient can speak clearly, the airway is intact. If not, consider these indications for emergency airway management:

  - **Structural airway damage:** Subcutaneous emphysema in neck, gurgling noises during breathing, or major facial trauma with blood in the airway
  - **Airway compression (see Fig. 2.16-16):** Dysphonia, stridor, expanding neck hematoma

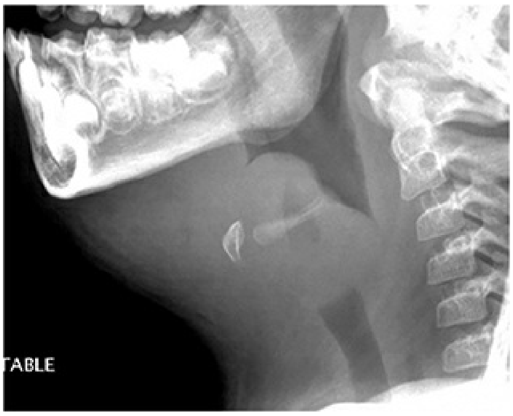


FIGURE 2.16-16. **Airway compression.** Lateral x-ray of the neck reveals a profoundly swollen epiglottis and complete airway obstruction. (Reproduced with permission from Charuvanij S, Houghton KM. Acute epiglottitis as the initial presentation of pediatric Systemic Lupus Erythematosus. *Pediatr Rheumatol Online J.* 2009 Oct 31;7:19. doi: 10.1186/1546-0096-7-19.)

  - **Somnolence:** Glasgow Coma Scale (GCS) score of 8 or less (see Table 2.16-13)

TABLE 2.16-13. **Glasgow Coma Scale Scoring**

SCORE	EYE OPENING RESPONSE (4 POINTS, "FOUR EYES")	VERBAL RESPONSE (5 POINTS, "JACKSON-5")	MOTOR RESPONSE 6 POINTS, "V6 ENGINE")
6			Follows commands
5		Oriented	Localizes pain
4	Spontaneous	Confused speech	Withdraws from pain
3	Opens to command	Inappropriate words	Abnormal flexion (decorticate)
2	Opens to pain	Incomprehensible	Abnormal extension (decerebrate)
1	None	None	None

- **Thermal or inhalation injury:** Should be suspected in patients with singed facial/nasal hairs, facial burns, or soot in the posterior oropharynx or sputum. Early airway management is indicated, as swelling of the airway with inflammation or with the administration of IV fluids may interfere with delayed intubation.
- **Management:** Emergency airway:
  - **Endotracheal intubation:** Preferred method, even in setting of cervical spinal trauma. If cervical spine trauma has not been ruled out, the patient should be immobilized during intubation.
  - **Nasotracheal intubation with fiberoptic bronchoscope:** Preferred if tracheobronchial tree is ruptured. This is contraindicated if there is basilar skull

  fracture (risk for intracranial penetration).
  - **Emergency cricothyroidotomy:** Attempted only if other methods are ineffective.
  - **Emergency tracheostomy:** In general, never to be done. The physician should choose cricothyroidotomy instead.

Breathing

- **Assessment:** Breath sounds, chest rise, oxygen saturation
- **Management:**
  - If patient has bilateral breath sounds and good chest rise but cannot oxygenate, intubate and mechanically ventilate.
  - If patient has unilateral breath sounds, think pneumothorax or hemothorax. Differentiate using percussion (dullness = hemothorax; resonance = pneumothorax). Can verify with CXR only if patient is hemodynamically stable. Insert chest tube to decompress lung and drain fluid accumulation in pleural space. If patient is hemodynamically unstable with a suspected tension pneumothorax, needle decompression is performed as a stabilizing measure until a chest tube is placed for definitive management.
  - If patient has unilateral breath sounds on the right after intubation, consider right mainstem bronchus intubation. Obstructive atelectasis of the left lung may occur with an endotracheal tube remaining in the right mainstem bronchus for an extended period. CXR may show the endotracheal tube below the carina. Withdraw the tube above the carina to ventilate both lungs.

Circulation

- **Assessment:** Evaluate for shock (systolic blood pressure [SBP] <90 mm Hg, fast and weak pulse, pallor, diaphoresis).
- **Management:** Three causes of shock in trauma are as follows:
  - **Hemorrhage** (most common): There are only five compartments that hold enough blood volume to cause shock: the chest, abdomen, pelvis, extremities, and floor (external hemorrhage). Intracranial hemorrhage (ICH) will never cause hypovolemic shock because herniation and death will occur before enough volume is lost to cause shock. Place two large-bore IVs (16 gauge or larger) and bolus 2 L isotonic crystalloid. If still unstable, transfuse packed RBCs and look for the source of bleeding. Transfuse 1 unit fresh frozen plasma (FFP) for every 4 units PRBCs given except in the case of severe trauma or obstetric bleeding. A 1:1:1 ratio of FFP:platelets:PRBCs is used for trauma patients requiring massive transfusion.
  - **Tension pneumothorax:** Diagnose clinically if hypotension, tracheal deviation, ↓ O_2 saturation, unilateral decreased breath sounds/hyperresonance. Needle decompression with IV catheter for immediate stabilization, and then place chest tube for definitive management. Do not wait for CXR to interven**e** (see Fig. 2.16-17).

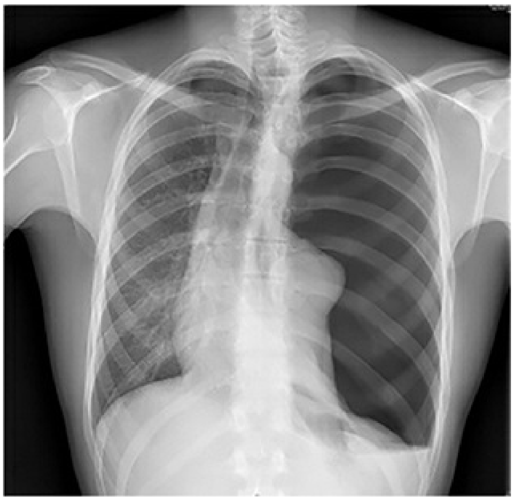


FIGURE 2.16-17. **Tension pneumothorax.** Note the hyperlucency of the affected (left) hemithorax, flattening and inferior displacement of the involved diaphragm, and shift of the mediastinal structures AWAY from the side of the pneumothorax. These are typical radiographic findings in patients with tension pneumothorax. (Reproduced with permission from Rosat A, Díaz C. Reexpansion pulmonary edema after drainage of tension pneumothorax. *Pan Afr Med J*. 2015;22:143 doi:10.11604/pamj.2015.22.143.8097.)

- **Cardiac tamponade:** Suspect if hypotension, muffled heart sounds, and jugular venous distention (Beck triad). Confirm with ultrasound (see Fig. 2.16-18). Surgical intervention can occur via pericardial window, pericardiocentesis, or thoracotomy.

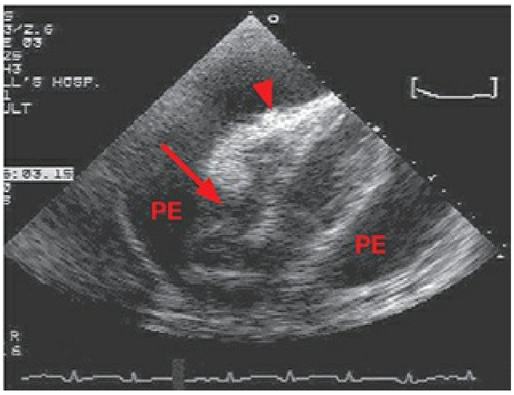


FIGURE 2.16-18. **Cardiac tamponade.** Echocardiogram in a patient with cardiac tamponade shows a large pericardial effusion with right atrial *(arrow)* and right ventricular *(arrowhead)* collapse. (Reproduced with permission from Hall JB et al. *Principles of Critical Care,* 3rd ed. New York, NY: McGraw-Hill; 2005.)

KEY FACT

When IV access is necessary but cannot be obtained after multiple attempts, place an interosseous line.

Deformities/Deficits

Assessment: Assess for traumatic brain injury using the GCS and pupillary examination. Assess for spinal cord injury by examining movement and gross sensation in extremities.

Exposure

- **Assessment:** Assess visible injuries, take body temperature, log-roll the patient to evaluate for spinal step-offs or deformities, and perform rectal exam to assess sphincter tone.
- **Management:** Remove clothing, and cover with warm blankets.

KEY FACT

A rough estimate of SBP can be made based on palpated pulses. Palpable carotid = 60 mm Hg, femoral = 70 mm Hg, and radial = 80 mm Hg.

SECONDARY SURVEY

After the patient's ABCDEs are managed, conduct a full head-to-toe exam.

Adjuncts to survey:

- Procure CXR, x-ray of the pelvis, and focused abdominal sonography for trauma (FAST) to screen for intra-abdominal or pericardial fluid.
- Pertinent labs should address mechanism of injury, intoxication or overdose, and medical history. Type and cross-match all patients of concern or with hemorrhage.
- Place urinary catheter to monitor urine output in hemodynamically unstable patients to guide resuscitation and in those undergoing surgery.
- Place orogastric tube for patients requiring mechanical ventilation.
- Order radiologic studies based on the assessment of hemodynamically stable patients:
  - CT of the head for any patient with head trauma, loss of consciousness, drowsiness/altered mental status, facial injuries, structural skull damage, or neurologic deficits.
  - Cervical spine (C-spine) CT needed for all patients <60 years of age who satisfy one of the National Emergency X-Radiography Utilization Study (NEXUS) criteria. Criteria include midline C-spine tenderness, altered mental status, intoxication, neurologic deficits, or distracting injuries. CT imaging is superior and preferred over x-ray for evaluation of C-spine fractures. If fracture is detected, proceed to image the full spine.

KEY FACT

The physician should always rule out urethral injury before placing a urinary catheter. Blood at the meatus, hematuria, difficulty voiding, high-riding prostate, and scrotal hematoma are signs of urethral injury. A retrograde urethrogram can identify the injury.

PENETRATING TRAUMA

This section describes management of specific trauma injuries after the initial evaluation using primary and secondary surveys. These considerations generally assume ABCDEs are previously secured.

HEAD

Cranium/Face

- Penetrating trauma to the cranium commonly occurs in conjunction with blunt injury and can be devastating to neurologic function. In the hemodynamically stable patient, emergent CT of the brain should be performed to assess the degree of intracranial injury.
- Facial lacerations should be evaluated for damage to nearby/underlying structures. Motor and sensory function of the facial and trigeminal nerves should be assessed. CT scan may be used to evaluate bony damage to the facial sinuses. Facial lacerations may generally be closed with primary intention after thorough washout.

Eyes

- Penetrating injury to the globe is commonly associated with intraocular foreign bodies. Exam findings consistent with globe laceration include visual deficits, gross deformity, volume loss of globe, teardrop-shaped pupil, leakage of vitreous humor, and a positive Seidel sign (clearing of fluorescein as aqueous humor leaks from the anterior chamber). Globe lacerations may be accompanied by hyphema of the anterior chamber and are often associated with orbital fractures.
- If there is suspicion for globe laceration, care must be taken to avoid placing any pressure on the globe, which leads to expulsion of intraocular contents. Avoid eyelid retraction, and do not perform tonometry. To prevent an increase of pressure within the globe and expulsion of intraocular material via vomiting or crying, patients are provided antiemetics, sedation, and pain control.
- Evaluation is performed with noncontrast CT through the orbits.
- Surgical repair should be pursued within 24 hours.
- Orbital fractures may be associated with entrapment of the inferior oblique and inferior rectus muscles, resulting in limited eye movement, and are visualized on CT imaging. The oculocardiac reflex may produce severe nausea and bradycardia, which warrants surgical release of the entrapped muscle.

Ears

- Evaluation of laceration should include assessment of middle ear injury, basilar skull fractures, injury to parotid gland, and function of facial nerve. Otorrhea may be tested for β-transferrin to assess for CSF leakage, and CT imaging of the temporal bone may be performed with suspicion of bony involvement.
- Primary closure is typically pursued as first-line management, especially with exposure of cartilaginous tissue. Coverage of cartilaginous tissue reduces risk of infection and ischemic necrosis.

Oral Cavity

- Evaluation of an intraoral laceration should include assessment of dental injury, fracture of the midface/maxilla, and mandibular fracture. CT imaging is preferred for midface and mandibular fractures.
- The internal carotid artery (ICA) may course directly posterior to the pharynx in certain anatomic variations. Stabbing injuries to the posterior pharynx or soft palate, typically seen in children who fall with pens or sticks in the oral cavity, may lead to traumatic dissection of the ICA.
- Gingival and buccal mucosal lacerations generally do not require primary closure and heal rapidly due to high vascularity. Primary closure is pursued if food particles may become trapped within the wound, if the wound is over 2 cm in length, or if there is tissue

overlying the occlusal surface.

Nasal Trauma

- Nasal lacerations are often accompanied by injury to the nasal bones. Physical examination of nasal injury should include inspection of gross alignment, palpation for bony abnormality, the presence of crepitus, visual inspection and palpation of possible septal hematoma, and detection of possible CSF drainage. CSF draining through the nasal cavity indicates fracture of the cribriform plate.
- **Septal hematoma:** Fluid between the mucoperichondrium and nasal septum results in pressure-related injury and necrosis to the poorly vascularized septal cartilage, which can lead to perforation. Fluid in this space also predisposes to abscess formation. Presence of a septal hematoma therefore requires urgent drainage and packing to prevent reaccumulation of fluid.
- A nasal laceration with exposed cartilaginous tissue is considered an indication for empiric antibiotic therapy.

Auricular Hematoma

- An auricular hematoma refers to a collection of blood typically following blunt trauma to the cartilaginous pinna of the external ear.
- Management should include prompt drainage and compression to prevent reaccumulation of hematoma.
- If an auricular hematoma is not fully drained, permanent fibrocartilaginous tissue will fill the space in which blood originally occupies, referred to as cauliflower ear.

Q 1

A 22-year-old woman is brought to the emergency department after a motor vehicle collision in which she was the restrained driver. She receives 2 L of crystalloid en route and has a BP of 65/40 mm Hg and a HR of 135 bpm on arrival. She has ↓ breath sounds on the right, flat neck veins, and dullness to percussion on the right side. What is the most likely diagnosis?

Q 2

A 25-year-old man walks into the emergency department holding a blood-soaked towel against his neck after being shot. The patient is anxious, appears pale, and states he heard multiple gunshots. Vital signs after 2 L of crystalloid are BP 86/55 mm Hg, HR 122 bpm, RR 16/min, and SpO_2 99%. Physical examination reveals that the neck wound does not extend through the platysma muscle. What is the next step in management?

NECK

- Patients with signs of arterial injury (eg, active bleed, expanding hematoma, neurologic deficit, or hematemesis) or hemodynamic instability require immediate fortification of the airway and transfer to the operating room for exploration.
- Stable patients should receive CT angiography (CTA) of the neck. Identified vascular injuries are treated with surgery or embolization.

- Patients with suspected injury to the trachea or esophagus (eg, gurgling breath sounds, bubbling wound, pneumomediastinum, crepitus) should be evaluated via direct visualization, using bronchoscopy or esophagoscopy. Alternatively, barium swallow esophagography can evaluate the esophagus.

KEY FACT

Only wounds that violate the platysma muscle are considered true penetrating neck trauma. Other superficial wounds are treated with conservative wound care.

CHEST

Penetrating chest injuries are often treated during the primary survey because they often compromise breathing or cause hemodynamic instability. Evaluation of additional penetrating chest injuries is discussed here.

History/PE

- If a previously stable chest trauma patient becomes rapidly unstable, suspect air embolism.
- A new diastolic murmur after chest trauma suggests aortic dissection associated with aortic valve insufficiency.
- Massive air leak into tube thoracostomy suggests tracheobronchial injury.

KEY FACT

Leave impaled objects in place until the patient is taken to the operating room, as such objects may tamponade further blood loss.

Diagnosis

- Procure a CXR for any patient with penetrating chest trauma to evaluate for pneumothorax or hemothorax not found in the primary survey. Aortic disruption, diaphragmatic tear, or esophageal injury may also be evident on CXR.
- Chest injuries between the nipples require evaluation of mediastinal structures. The physician should order echocardiography for the heart, CTA for the aorta and its branches, bronchoscopy for the upper airway, and esophagograph/esophagogram for the esophagus.

Treatment

- Pneumothorax or hemothorax requires placement of a tube thoracostomy.
- Initial output of 1500 mL or an output of 300 mL/hr for 3 consecutive hours from the tube thoracostomy warrants operative thoracotomy.
- Aortic, diaphragmatic, esophageal, or tracheobronchial injury also warrants surgical correction.
- Immediate thoracotomy without transport to the operating room may be indicated for patients with penetrating chest trauma and witnessed cardiac arrest.

Hemothorax is the most likely diagnosis. Hemodynamic instability with ↓ breath sounds are concerning for hemothorax and tension pneumothorax. Flat neck veins are more consistent with hemothorax because tension pneumothorax causes ↑ intrathoracic pressure → ↓ ventricular filling → ↑ CVP and distended neck veins. Dullness to percussion also shifts the diagnosis toward hemothorax. Each hemothorax can hold 40% of a patient's circulating blood volume, and patients may therefore present in hypovolemic shock.

2 A

Administer blood products, and search for a source of bleeding other than the neck. The management of this patient begins with the primary survey. The patient can speak, so airway is intact. RR and SpO_2 are within normal limits, so breathing is assumed to be stable. The patient remains hemodynamically unstable despite 2 L of crystalloid, so blood products are administered, and a source of bleeding is sought. The platysma is not violated, so the neck wound is not the cause of significant bleeding despite the blood-soaked towel. There is likely an additional gunshot wound that needs to be identified.

ABDOMEN

Penetrating trauma to the abdomen is defined as any object (typically gunshot or knife) that violates the peritoneum. An important step in management is determining whether peritoneal signs (guarding, rigidity, rebound tenderness) are present. These injuries are managed according to the mechanism:

- Gunshot wounds below the nipple (fourth intercostal space) require immediate exploratory laparotomy.
- Abdominal stab wounds warrant immediate exploratory laparotomy if the patient exhibits hemodynamic instability, peritoneal signs, or extruded bowel or omentum.
- If the patient does not have these indications, explore the wound to identify violation of the peritoneum. If a defect is found, laparotomy is generally indicated.
- If the peritoneum is not violated, observe the patient for 24 hours. Perform a laparotomy if the patient develops hemodynamic instability, peritoneal signs, leukocytosis, or a drop in Hb >3 mg/dL.

EXTREMITIES

Evaluation of a penetrating injury to the extremities should include an assessment of the soft tissue, bony skeleton, and neurovascular function. Multiple injuries are usually present.

Neurovascular Injuries

- Check pulses using palpation and Doppler to evaluate for vascular injury.
- Evaluate motor and sensory function of the extremity.
- For hard signs of vascular injury (eg, expanding hematoma, pulsatile bleeding, absent pulse), immediately explore and repair in the operating room.
- For soft signs of vascular injury (neurologic deficit, significant bleeding, weak pulse), perform CTA.

Orthopedic Injuries

- Extremities with multiple injuries are generally treated in the following order:
  1. Fixation/reduction of broken bones.
  2. Revascularization of arterial injuries. If arteries are repaired prior to bone fixation/reduction, there is risk of reinjury to repaired vessels with the jagged bone edges during fracture reduction.
  3. Reapproximation of injured nerves.
  4. If an injury separates an appendage from the body, parts should be placed in gauze moistened with saline, sealed inside a plastic bag, and placed on ice to maximize tissue viability.
  5. Contaminated wounds require early wound irrigation and tissue debridement. Also, administer antibiotics and tetanus prophylaxis.
- Long-term complications include high-output heart failure caused by formation of an arteriovenous fistula (AVF). Despite ↑↑ cardiac output, patients present with signs and signs and symptoms of congestive heart failure (CHF).

Postamputation Pain

- **DVT:** In up to 50% of patients with lower extremity amputation
- **Stump hematoma:** Higher risk for patients on antithrombotic therapy
  - Stump pain: Caused by stump ischemia, neuroma formation, or infection
  - Neuroma: Localized pain; neuroma can be blocked with anesthetic injection
- **Infection:** Osteomyelitis, graft infection
- **Phantom limb pain:** Diagnosis of exclusion; commonly described as a burning, aching, electric-type pain
  - Can try treatment with gabapentin, ketamine, amitriptyline, or lidocaine
  - Other treatments: Mirror therapy, peripheral nerve stimulation, and virtual reality

BLUNT AND DECELERATION TRAUMA

HEAD AND FACE

Evaluate for signs of ↑ intracranial pressure ([ICP], eg, bradycardia, hypertension, respiratory depression, fixed and dilated pupil[s], vomiting, and/or papilledema). Treat ↑ ICP with head elevation, hyperventilation, and IV mannitol.

Linear Skull Fractures

Treat nonoperatively with wound care and closure if open. Surgery is reserved for displaced or comminuted fractures.

Epidural Hematomas

Lenticular or biconvex shape on CT of the head (see Fig. 2.16-19A). Blood from the middle meningeal artery fills the potential space between the dura and skull. These hemorrhages cannot cross suture lines (the dura is anchored to sutures), but can expand rapidly, causing uncal herniation and death. Patients classically lose consciousness immediately after the injury and undergo a “lucid interval” after which they become comatose. Examination may show ipsilateral blown pupil and ipsilateral hemiparesis. The condition calls for an emergent craniotomy.

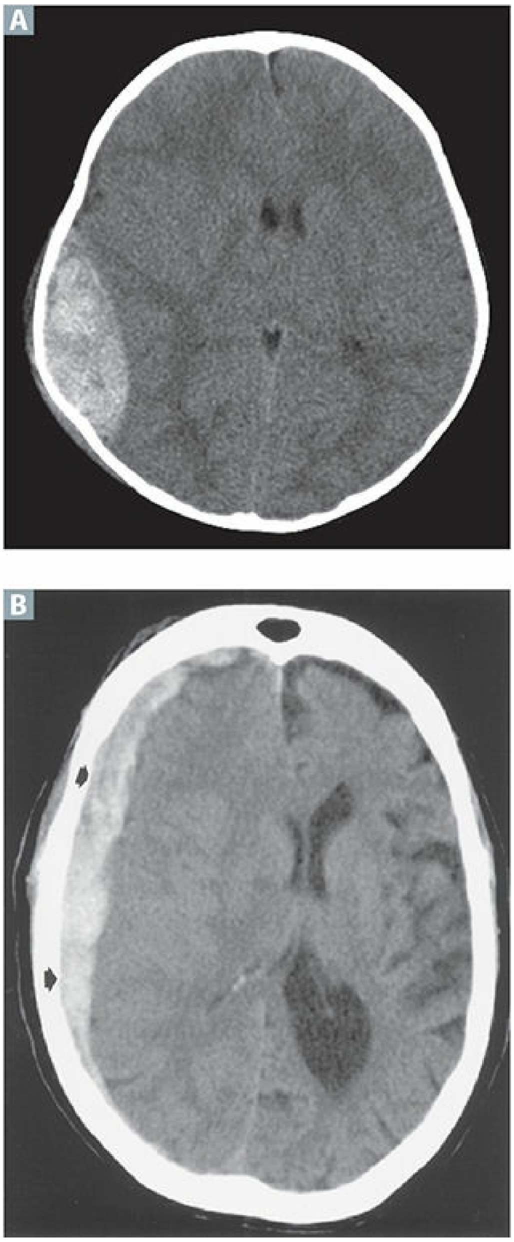


FIGURE 2.16-19. **Acute epidural and acute subdural hematoma. (A)** Noncontrast CT showing a right temporal acute epidural hematoma. Note the characteristic biconvex shape. **(B)** Noncontrast CT demonstrating a right acute hemispheric subdural hematoma. Note the characteristic crescentic shape. (Image A reproduced with permission from Doherty GM. *Current Diagnosis & Treatment: Surgery*, 13th ed. New York, NY: McGraw-Hill; 2010. Image B reproduced with permission from Chen MY et al. *Basic Radiology.* New York, NY: McGraw-Hill; 2004.)

Subdural Hematomas

Crescent-shaped bleed on CT of the head (see Fig. 2.16-19B). Blood from the dural bridging veins fills the potential space between the dura and arachnoid mater. These hemorrhages cross suture lines**.** They may present as acute (immediate), subacute (days), or chronic (weeks). Perform craniotomy if CT shows midline shift or patient develops worsening neurologic symptoms or mental status. Otherwise, manage ICP and use fluids judiciously to limit cerebral edema.

Diffuse Axonal Injury

A pattern of traumatic brain injury (TBI), especially following high-speed motor vehicle accidents. Accelerating and decelerating shear forces on the white matter tracts of the brain lead to microscopic or gross damage to the brain at the junction of the gray and white matter.

Treatment: Resuscitation of the patient, and once the injury has settled, rehabilitation for maximal functional outcome. Supportive measures and prevention of secondary injuries are the goals of long-term therapy.

Basilar Skull Fracture

- The basilar skull includes the ethmoid bone, orbital plate of frontal bone, petrous or squamous temporal bone, sphenoid, and occipital bones.
- A basilar skull fracture is associated with high-impact, blunt-force trauma; the fracture most commonly involves the temporal bone.
- Fractures including the temporal bone are highly associated with epidural hematomas because of proximity to the middle meningeal artery.
- Signs of basilar skull fractures include postauricular or mastoid ecchymosis (Battle sign), periorbital ecchymosis (raccoon eyes), clear rhinorrhea or otorrhea (CSF leak), and hemotympanum.
- A CSF leak may be tested by placing a drop of rhinorrhea or otorrhea onto an absorbent surface. It is positive if there is a concentration of blood in the center with a lighter stain of CSF surrounding the blood. β-Transferrin is tested to confirm the presence of CSF.
- All patients with basilar skull fractures are hospitalized to allow monitoring for altered mental status or progression of intracranial bleeding. Most basilar skull fractures will heal spontaneously, requiring no treatment. However, an associated CSF leak persisting for more than 7 days should be repaired operatively because of the significantly increased risk of meningitis without repair.

Pediatric Traumatic Brain Injury

- Falls, motor vehicle collisions (MVCs), and abuse are prevalent mechanisms of TBI in the pediatric population.
- Typically, workup is pursued after a high-risk mechanism of injury. However, some children without an obviously high risk for TBI should still be evaluated. Children with a history of significant loss of consciousness, altered mental status, vomiting, headache, and progression of symptoms should be evaluated for TBI, similar to patients with a high-risk mechanism of injury.
- Evaluation of a TBI includes a detailed neurologic examination, assigning a GCS score, and may include imaging of the brain with a CT scan. A CT of the head may initially be normal even in patients with obvious TBI from clinical history. These patients should be evaluated with an MRI, which is more sensitive for diffuse axonal injury and cerebral edema. The physician should intubate patients with a GCS score of 8 or less.
- Children with TBI have a high risk of cervical spine injury and must be placed in a cervical collar. It is typically difficult to rule out this type of injury in TBI patients due to altered mental status with or without sedation.
- Diffuse axonal injury (DAI) may occur with acceleration or deceleration forces caused by shearing forces between the gray and white matter. DAI causes global injury to the brain and may result in coma. The mechanism of DAI in children includes falls, MVCs, and abuse such as shaken baby syndrome.
- TBIs in the pediatric population may be accompanied by brain contusion, intraparenchymal hemorrhage, subdural hematoma, epidural hematoma, subarachnoid hemorrhage, and/or brain herniation.
- After the initial injury, children with TBI experience decreased cerebral perfusion and

increased metabolic demand. The combination of lower oxygen supply and higher oxygen demand increases the risk for secondary hypoxic injury.

- Diffuse cerebral swelling is observed more frequently in the pediatric population, compared to adults, via poorly understood mechanisms.
- Management includes monitoring of blood pressure and ICP to ensure cerebral perfusion. Diligent fluid resuscitation and avoidance of antihypertensives are pursued to avoid hypoperfusion and secondary ischemic brain injury.

Le Fort Fractures

- The Le Fort grading system is used for fractures of the midface, which extend posteriorly through the pterygoid plates and separate the maxilla from the cranium. All of the Le Fort fractures run through the pterygoid plates, and classification is based on the different fracture patterns in the anterior bones of the midface.
- Airway compromise due to maxillary impaction is a significant concern with these fractures. Urgent management would involve disimpaction of the displaced segment and reassessment of the airway.
- Le Fort I fractures are transverse fractures through the maxilla, inferior to the zygoma. Physical examination is notable for mobility of the maxilla with rocking maneuvers and malocclusion.
- Le Fort II fractures are pyramidal fractures involving the nasal bridge, lacrimal bones, medial orbital floor, and lateral wall of the maxillary sinus.
- Le Fort III fractures run transversely from the nasal bridge, through the orbits, and involve the frontozygomatic suture. These injuries are commonly associated with basilar skull fractures. Physical examination is notable for complete instability of the midface on rocking maneuvers.
- These fractures warrant open reduction and surgical fixation of the midface after management of more urgent or life-threatening associated injuries. Reapproximation of dental occlusive surfaces is a major goal of reduction and fixation. If the mandible is also displaced, then the maxilla is fixed, based on the superior bony structures as a baseline, and the mandible is reduced to approximate with the occlusive surfaces of the maxilla.
- After fixation, patients are placed on a liquid diet and advanced appropriately.

Q

A 10-year-old boy is brought to the emergency department (ED) 5 hours after he hit his head on a concrete sidewalk while skateboarding. He did not lost consciousness. His neurologic exam is intact, and he reports mild pain in his head where the impact occurred. What is the next step in ED management?

CHEST

Tracheobronchial Disruption

Tracheobronchial disruption is most often caused by deceleration shearing forces.

- Physical findings include respiratory distress, hemoptysis, sternal tenderness, and subcutaneous emphysema.
- Radiographs may show a large pneumothorax or pneumomediastinum (see Fig. 2.16-20).

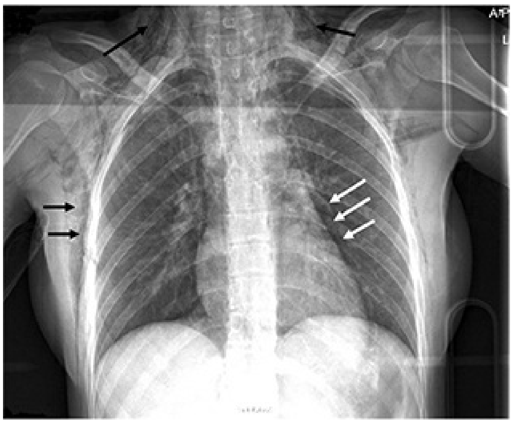


FIGURE 2.16-20. **CXR reveals pneumomediastinum *(white arrows)* and subcutaneous emphysema *(black arrows)*.** (Reproduced with permission from van Heijl M, Saltzherr TP, van Berge Henegouwen MI, Goslings JC. Unique case of esophageal rupture after a fall from height. *BMC Emerg Med.* 2009 Dec 15;9:24. doi: 10.1186/1471-227X-9-24.)

- A persistent air leak may be present when the chest tube when hooked to wall suction.

Pulmonary Contusion

Associated with thoracic trauma and generally appearing within 24 hours. A pulmonary contusion may lead to hypoxia from damage to capillaries, causing interstitial fluid accumulation. Hypoxia therefore tends to worsen with fluid hydration.

- Look for patchy unilateral infiltrates on CXR, not restricted by lobar anatomy.
- Intubate if necessary and be judicious about IV fluids. Noninvasive positive-pressure ventilation may also be used.
- It is more common in children because of a less rigid, protective chest wall.

Flail Chest

Three or more adjacent ribs are fractured at two points, causing paradoxical movement of the segment. The segment moves **in**ward with **in**spiration and outward during exhalation (see Fig. 2.16-21).

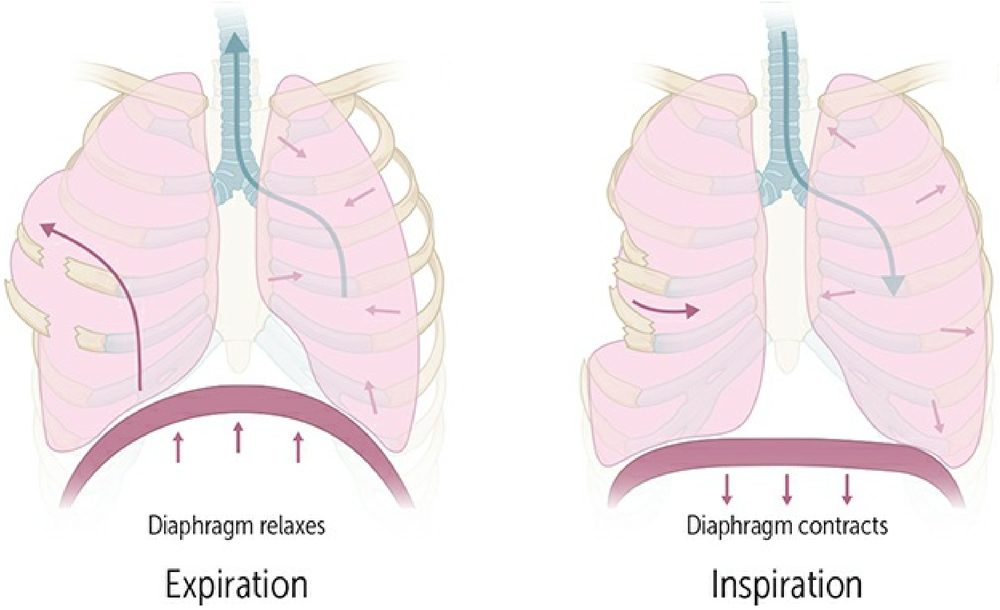


FIGURE 2.16-21. **Flail chest.** (Reproduced with permission from USMLE-Rx.com.)

- Respiratory compromise in flail chest occurs because of underlying pulmonary contusion rather than the flail chest itself.
- Pain control and positive-pressure ventilation compose the mainstay of treatment for flail chest. Ribs can be fixed surgically, especially in severe cases.

KEY FACT

The first rib, scapula, and sternum are thick, strong bones and difficult to break. Blunt trauma causing these fractures is associated with aortic disruption.

Unilateral Diaphragmatic Paralysis

- Note that the phrenic nerve courses from C3 to C5 in the neck, wraps around the anterior scalene muscle, and then travels over the anterior pericardium before innervating the diaphragm. Injury to any of these regions could therefore cause injury to the phrenic nerve.
- Patients may be asymptomatic, experience increased exertional dyspnea or orthopnea, or have decreased exercise tolerance.
- Unilateral diaphragm paralysis is more common and may be seen as an incidental finding on imaging without any related complaints. Bilateral disease is more likely to be observed in the context of muscular disorders.
- A diagnosis of unilateral paralysis would be suspected with an elevated hemidiaphragm (Fig. 2.16-22) on upright CXR and is confirmed with a fluoroscopic sniff test. This test observes a paradoxical elevation of the paralyzed hemidiaphragm during forceful inspiration (sniffing). Bilateral paralysis is diagnosed with clinical history and is aided by reduced forced vital capacity (FVC) on pulmonary function tests.

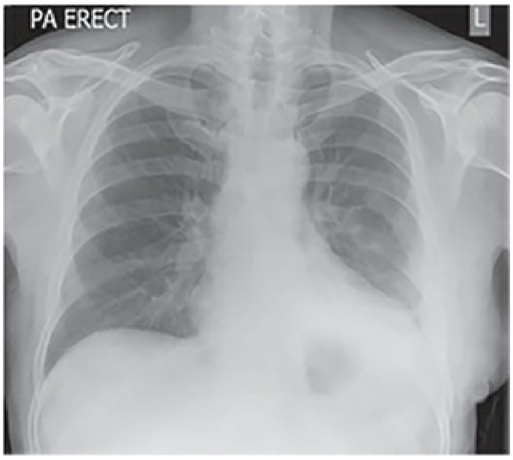


FIGURE 2.16-22. Left diaphragmatic paralysis. Chest x-ray displaying elevation of the left hemidiaphragm with displacement of bowels into the left hemithorax. (Reproduced with permission from Elshafie G, Acosta J, Aliverti A, et al. Chest wall mechanics before and after diaphragm plication. *J Cardiothorac Surg*. 2016;11:25. Published 2016 Feb 2. doi:10.1186/s13019-016-0419-x.)

- Unilateral paralysis may not require any treatment. Patients requiring intervention may be treated with surgical plication, which tightens the hemidiaphragm and prevents negative thoracic pressure from upwardly displacing the paralyzed diaphragm during inspiration, allowing for more efficient air movement into the lungs. Treatment may involve ventilatory support.
- Bilateral paralysis usually requires ventilatory support. Stimulation of the phrenic nerve

with a pacemaker device is suitable for certain candidates with bilateral diaphragmatic paralysis and an intact phrenic nerve.

A

Discharge the patient. If GCS is over 14, patients with loss of consciousness can be observed with instructions to return immediately if neurologic symptoms develop.

Diaphragm Rupture

- Injury to the diaphragm is rare and typically associated with penetrating or blunt injuries to the abdomen or thorax. The left hemidiaphragm is more commonly injured than the right, which is possibly because of the protective effect of the liver under the right hemidiaphragm.
- Penetrating injuries to the diaphragm generally result in smaller perforations and are therefore more likely to remain undetected, compared to blunt abdominal trauma, which results in large tears. Blunt force to the abdomen or chest increases pressure in the abdominal or thoracic cavity and distends the diaphragm, leading to rupture.
- Any blunt-force trauma to the abdomen or chest and any penetrating injury between the T4 and T12 dermatomes should raise suspicion of diaphragmatic injury.
- Diagnosis is frequently made using CT imaging while assessing for life-threatening injuries or hemorrhage. However, smaller tears may not be visible. Ultrasound may visualize discontinuity of the diaphragm during FAST scans, and upright CXR may show herniation of abdominal contents into the hemithorax.
- If suspicion for diaphragm rupture is high, laparoscopic exploration is pursued.
- Diaphragm rupture may be associated with herniation of abdominal or thoracic contents, diaphragm paralysis, rib fractures, pulmonary contusion, atelectasis, or biliary fistula.
- After diagnosis, all diaphragm ruptures on the left side are surgically repaired. Right-sided diaphragm ruptures are first managed nonoperatively, because the liver tamponades the injury and decreases the risk for developing complications of the rupture.

BLUNT CARDIAC INJURY

Also known as myocardial contusion, blunt cardiac injury may present as a new bundle branch block, ectopy or dysrhythmia, or hypotension.

- Severe contusion can present with left ventricle (LV) dysfunction and cardiogenic shock. Serum cardiac biomarkers are often elevated.
- Treatment is largely supportive, sometimes requiring inotropes.

Q 1

A 44-year-old woman is brought to the emergency department following a motor vehicle collision. On arrival, her BP is 70/35 mm Hg and her heart rate 110 bpm. Physical examination reveals bruises over the chest and abdomen. A pulmonary artery catheter is placed and reveals a pulmonary capillary wedge pressure (PCWP) of 16 mm Hg. After resuscitation with 2 L of crystalloid, BP and heart rate measurements are 80/40 mm Hg and 125 bpm, respectively. PCWP is now 24 mm Hg. What is the most likely diagnosis?

Q 2

A 36-year-old man is brought to the emergency department following a motor vehicle collision in which he was an unrestrained passenger. X-rays show multiple fractures. Several hours later he develops fever, respiratory distress, and a rash consisting of small red and purple 1- to 2-mm macules covering his arms and shoulders. What is the most likely diagnosis?

Aortic Disruption

Aortic disruption is classically caused by rapid deceleration injury (eg, high-speed motor vehicle accidents, ejection from vehicles, fall from heights).

- Injury is most common in the proximal thoracic aorta near the ligamentum arteriosum, which anchors the aorta in place. The adjacent aorta displaces forward, creating shear force.
- CXR reveals a widened mediastinum, loss of aortic knob, pleural cap, deviation of the trachea and esophagus, and depression of the left mainstem bronchus (see Fig. 2.16-23).

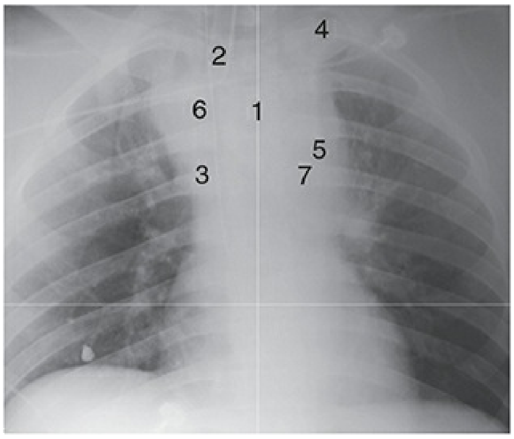


FIGURE 2.16-23. **Aortic disruption.** CXR of hypotensive man injured in a high-speed motor vehicle collision. Findings include *(1)* widened mediastinum; *(2)* deviation of the trachea to the right; *(3)* widening of the right paratracheal stripe; *(4)* left apical cap; *(5)* blurring of the aortic knob; *(6)* deviation of the nasogastric (NG) tube to the right; and *(7)* obliteration of the aortopulmonary window. (Reproduced with permission from Stone CK, Humphries RL. *Current Diagnosis & Treatment: Emergency Medicine*, 7th ed. New York, NY: McGraw Hill; 2011.)

- Ultrasonography can diagnose concurrent pericardial tamponade.
- Confirm with CTA in stable patients. Unstable patients may undergo transesophageal echocardiogram or intraoperative evaluation.
- Emergency surgery is required for any defect.

KEY FACT

Because complete aortic rupture is rapidly fatal (85% die at the scene), patients with aortic disruption seen in the emergency department usually have a contained hematoma within the adventitia.

KEY FACT

Hoarseness of the voice can be caused by aortic disruption as expansion of the hematoma impinges on the left recurrent laryngeal nerve.

ABDOMEN

While management of specific organ damage is beyond the scope of Step 2 CK, some common associations come in handy (see Table 2.16-14). Figure 2.16-24 describes the diagnostic workup for blunt abdominal trauma (BAT). The FAST exam is preferred over diagnostic peritoneal lavage (DPL) in unstable patients, but DPL is used for unequivocal FAST or if FAST is unavailable. Assess hemodynamically stable patients with CT scan. Patients with minor BAT (no seatbelt sign [see Fig. 2.16-25], mild tenderness) may be observed with serial abdominal scans.

TABLE 2.16-14. Commonly Injured Abdominal Organs

ORGAN	NOTES
Spleen	Most commonly injured organ in BAT Often associated with fractured left ribs 9–11 Give vaccines 2 weeks later if spleen is removed (pneumococcal [pneumococcal vaccine (PCV) and pneumococcal polysaccharides vaccine (PPSV)], *Haemophilus influenzae* type b [Hib], and meningococcal)
Liver	Second most commonly injured organ in BAT Often associated with right lower rib fractures
Kidney	May present with gross or microscopic hematuria
Duodenum	Susceptible to compression injury caused by position adjacent to spinal column; look for retroperitoneal air on x-ray Suspect duodenal hematoma in a child who wrecks their bike and falls on handlebars; patient presents with epigastric pain + bilious vomiting
Pancreas	Also common in children with handlebar injuries
Diaphragm	Diaphragm most commonly ruptures on the left because liver protects the right side Look for abdominal viscera in thorax on CXR

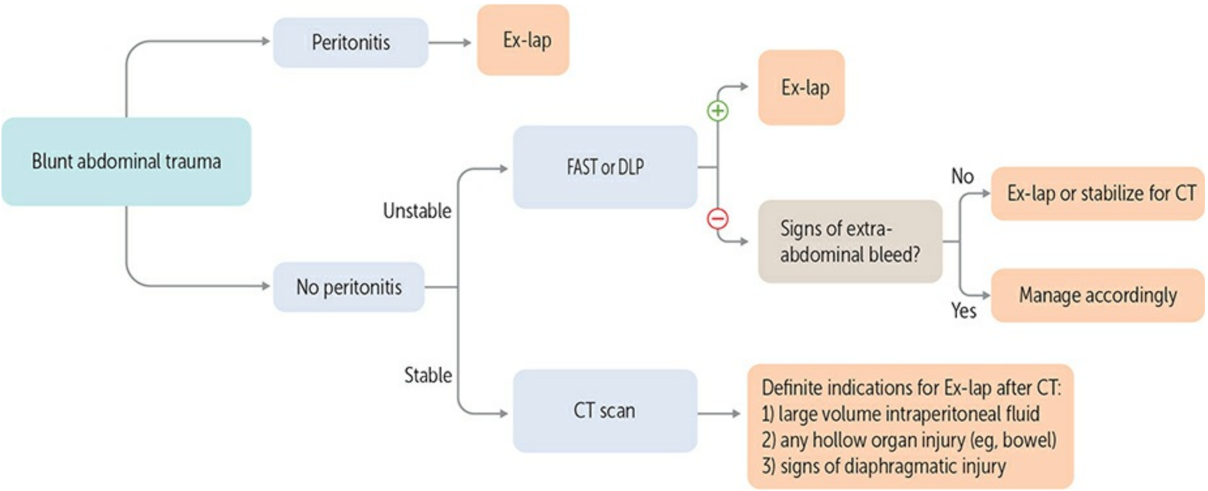

Blunt abdominal trauma
Peritonitis
Ex-lap
No peritonitis
Unstable
Stable
FAST or DLP
Ex-lap
Signs of extra-abdominal bleed?
No
Ex-lap or stabilize for CT
Yes
Manage accordingly
CT scan
Definite indications for Ex-lap after CT:
1) large volume intraperitoneal fluid
2) any hollow organ injury (eg, bowel)
3) signs of diaphragmatic injury

FIGURE 2.16-24. **Blunt abdominal trauma algorithm.** (Reproduced with permission from USMLE-Rx.com.)

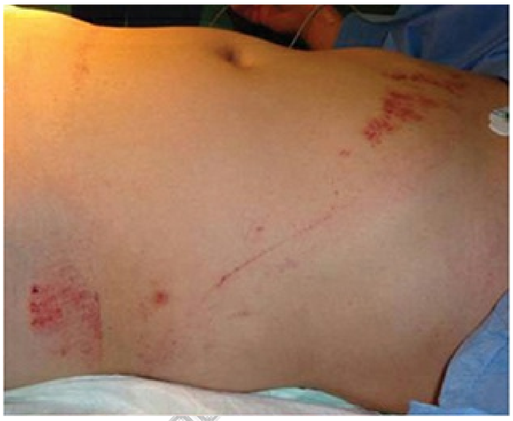


FIGURE 2.16-25. **Seat belt sign.** Adult restrained driver with abdominal seat belt sign. (Reproduced with permission from Abbas AK, Hefny AF, Abu-Zidan FM. Seatbelts and road traffic collision injuries. *World J Emerg Surg* 2011;6:18.)

- Anticoagulation and cardiac catheterization place patients at risk for retroperitoneal hematoma. Look for back pain, flank bruising, and hemodynamic instability.

1 A

The most likely diagnosis is cardiogenic or obstructive shock probably caused by severe blunt trauma to the chest. The patient has signs of shock, and her ↑ PCWP suggests either a cardiogenic or an obstructive cause. Based on the mechanism of injury, she may have severe myocardial contusion or cardiac tamponade.

2 A

Fat embolism. The classic presentation of fat embolism is fever, tachypnea, tachycardia, conjunctival hemorrhage, and upper extremity petechiae after a patient suffers long-bone fractures.

- In patients with spinal cord injuries, urinary catheter placement is diagnostic and therapeutic for acute urinary retention.

PELVIS

Pelvic Fractures

Most commonly occur after high-speed traumas such as motor vehicle accidents or falls from heights. Can cause significant hemorrhage, leading to hypotension and shock.

Diagnosis

- Apply pressure to the anterior superior iliac spine bilaterally to test for unstable or open book fracture.
- X-ray of the pelvis may confirm the fracture. In a stable patient, CT scan of the pelvis will better define the extent of injury.
- Always rule out injuries to other pelvic structures. Perform rectal examination and/or proctoscopy for the rectum, retrograde cystogram for the bladder, pelvic exam for the vagina in women, and retrograde urethrogram for the urethra in men.

KEY FACT

Marfan syndrome, syphilis, and Ehlers-Danlos syndrome weaken the aortic wall and predispose to aortic injury.

KEY FACT

Diaphragmatic irritation can cause referred pain to the shoulder because the phrenic nerve shares origins with the brachial plexus. Irritation is caused by blood, air, or rupture.

KEY FACT

Because of the ringlike structure of the pelvic anatomy, pelvic fractures tend to occur in multiples rather than singular fractures.

Treatment

- Transfuse patients as necessary. More than 40% of patients with pelvic fractures require transfusions.
- Management of unstable patients is controversial, but placement of an external pelvic binder over the trochanters (provides stability and tamponade effect) and angiographic embolization probably constitute the safest approach.
- External and internal pelvic fixations are also options, but surgery on a bleeding pelvis is risky. This may be the answer in a stable patient or if a pelvic binder is not an option.

Rectus Sheath Hematoma

Rectus sheath hematomas arise from hemorrhage of the deep inferior epigastric artery as it inserts into the rectus abdominis muscle and are contained within the rectus abdominis muscle as well as surrounding fascia.

- Below the arcuate line, the posterior aspect of the rectus abdominis muscle is no longer supported by the posterior rectus sheath, which predisposes the vessels inserting into the inferior muscle to experience larger shear forces. For this reason, most rectus sheath hematomas are located in the inferior abdomen.

- Rectus sheath hematomas present as acute-onset abdominal pain, an abdominal mass, and constitutional symptoms. Patients may also report back or leg pain. Carnett and Fothergill signs on physical examination help to differentiate the abdominal wall from the abdominal cavity as the origin of pathology.
- **Carnett sign:** Carnett sign is positive when the point of maximum tenderness is unchanged when moving the patient from a supine to upright position.
- **Fothergill sign:** Fothergill sign is positive if the mass does not cross the midline and does not move with movement of the lower extremities.
- Diagnosis is confirmed with CT imaging of the abdomen and pelvis.
- Patients should be treated similarly to any patient with acute blood loss. Monitor hemodynamic status and assess the need for fluid resuscitation or transfusion of RBCs.
- Patients are treated with CT-guided surgical evacuation of the hematoma and ligation of actively bleeding vessels.
- Patients have drains held to suction during the postoperative period to prevent reaccumulation of the hematoma.

Bladder Injuries

Classified based on whether the injury communicates with the peritoneal cavity (intraperitoneal) or stays confined to the pelvis (extraperitoneal).

- **Extraperitoneal bladder injury:** Rupture of bladder neck/trigone. Pain is localized in the lower abdomen and pelvis. Causes gross hematuria. Treat nonoperatively with Foley catheter.
- **Intraperitoneal bladder injury:** Rupture of the dome of the bladder. Abdominal pain is diffuse ± guarding and rigidity. Urine output is low or absent despite aggressive rehydration. Treat with surgical correction.

Urethral Injury

Injury to the urethra is mostly seen in young males and can be categorized as either anterior or posterior.

- Insertion of a urethral catheter in a patient with suspected genitourinary injury before retrograde urethrography is contraindicated due to possible exacerbation of urethral injury during insertion.
- Patients present with blood at the meatus, high-riding prostate, difficult urination, pelvic fractures, and associated genital or abdominal injuries.
- The anterior urethra is defined as the penile and bulbar urethra. Injury to the anterior urethra is seen with penetrating trauma to the penis, penile fractures, and straddle injuries. A urethral or suprapubic catheter is placed for bladder drainage. If tissue damage is significant or urethral repair is planned for a later date, then urine should be diverted proximal to the site of the injury via urethrostomy or suprapubic catheter.
- The posterior urethra is defined as membranous and prostatic urethra. Injury to the posterior urethra is most common in association with pelvic fractures. The membranous urethra is the most susceptible segment of the entire urethra due to higher mobility and vulnerability to shear forces. Partial posterior urethra injuries are managed with urinary catheters. Complete injuries are first managed with suprapubic tubes, followed by surgical repair.

Rectal and Vaginal Injuries

Usually managed nonoperatively unless reconstruction is necessary.

HIGH-YIELD FACTS IN

RAPID REVIEW

Cardiovascular

Dermatology

Endocrinology

Epidemiology

Health Systems Science

Gastrointestinal

Hematology

Musculoskeletal

Neurology

Obstetrics

Gynecology

Pediatrics

Psychiatry

Pulmonary

Renal/Genitourinary

Multisystem

CARDIOVASCULAR

Prolonged QT + syncope + sensorineural deafness	Jervell and Lange-Nielsen syndrome
Murmur—hypertrophic obstructive cardiomyopathy	Systolic ejection murmur heard along lateral sternal border that ↑ with ↓ preload (valsalva maneuver)
Murmur—aortic insufficiency	Austin Flint murmur, a diastolic, decrescendo, low-pitched, blowing murmur that is best heard sitting up; ↑ with ↑ afterload (handgrip maneuver)
Murmur—aortic stenosis	Systolic crescendo-decrescendo murmur that radiates to neck; ↑ with ↑ preload (squatting maneuver)
Murmur—mitral regurgitation	Holosystolic murmur that radiates to axilla; ↑ with ↑ afterload (handgrip maneuver)
Murmur—mitral stenosis	Diastolic, mid to late, low-pitched murmur preceded by an opening snap
Classic ECG finding in atrial flutter	"Sawtooth" P waves
Drugs that slow heart rate	β-blockers, calcium channel blockers, digoxin, amiodarone
Treatment for atrial fibrillation and atrial flutter	If unstable, cardiovert If stable or chronic, rate control with CCBs or β-blockers Anticoagulation may be indicated for stroke prevention
Treatment for ventricular fibrillation	Initiate CPR and immediate defibrillation
Short PR interval and slurred upstroke of QRS. What antiarrhythmics are contraindicated	AV nodal blockers (can cause preferential conduction down accessory pathway and unstable arrhythmias)
Most common cause of cardioembolic stroke	Atrial fibrillation
Management of symptomatic bradycardia	Initially atropine, temporary pacing if refractory to medication
Only medications that reduce mortality in HF with preserved EF	Empagliflozin and dapagliflozin
Medications that provide mortality benefit in HF with reduced EF	ACE inhibitors/ARBs, ARNIs, β-blockers, spironolactone, hydralazine + isosorbide dinitrate (in Black patients)
Diagnostic test for hypertrophic cardiomyopathy	Echocardiogram (showing a thickened left ventricular wall and outflow obstruction)
Young patient with family history of sudden death collapses and dies while exercising	Hypertrophic cardiomyopathy
Young patient with angina at rest and ST-segment elevation with normal cardiac enzymes	Prinzmetal angina
Definition of unstable angina	Angina that is new or worsening with no ↑ in troponin level

Appropriate diagnostic test?	
▪ 50-year-old man with stable angina can exercise to 85% of maximum predicted heart rate	Exercise stress treadmill with ECG
▪ 65-year-old woman with left bundle branch block and severe osteoarthritis has unstable angina</bl>	Pharmacologic stress test (eg, dobutamine echocardiogram)
Signs of active ischemia during stress testing	Angina, ST-segment changes on ECG, or ↓ BP
ECG findings suggesting MI	ST-segment elevation or depression, flattened T waves, and Q waves
Coronary territories in MI	Anterior wall (LAD/diagonal), inferior (PDA), posterior (left circumflex/oblique, RCA/marginal), septum (LAD/diagonal)
Common symptoms associated with silent MI	CHF, shock, altered mental status, unexplained fatigue, heartburn, shortness of breath, discomfort in the neck or jaw, and indigestion
Treatment for acute coronary syndrome	ASA, heparin, clopidogrel, morphine, O_2, sublingual nitroglycerin, IV β-blockers
Dressler syndrome	Autoimmune reaction with fever, pericarditis, and ↑ ESR occurring 2–4 weeks post-MI
Hypercholesterolemia treatment that leads to flushing and pruritus	Niacin
Metabolic syndrome	Abdominal obesity, high triglycerides, low HDL, hypertension, insulin resistance, prothrombotic or proinflammatory states
Antihypertensive for a diabetic patient with proteinuria	ACE inhibitor/ARB
Eight surgically correctable causes of hypertension	Renal artery stenosis, coarctation of the aorta, pheochromocytoma, Conn syndrome, Cushing syndrome, unilateral renal parenchymal disease, hyperthyroidism, hyperparathyroidism
Beck triad for cardiac tamponade	Hypotension, distant heart sounds, and JVD
Pulsus paradoxus	In systolic BP of >10 mm Hg with inspiration; seen in cardiac tamponade
Classic ECG findings in pericarditis	Low-voltage, diffuse ST-segment elevation
Water bottle–shaped heart	Pericardial effusion; look for pulsus paradoxus
Endocarditis prophylaxis regimens	Oral surgery—amoxicillin for certain situations GI or GU procedures—not recommended
Prolonged PR interval in infective endocarditis suggests	Possible aortic root abscess
Classic physical findings for endocarditis	Fever, heart murmur, Osler nodes, splinter hemorrhages, Janeway lesions, Roth spots
Duke criteria for endocarditis	Major: Positive blood cultures, new murmur, positive echocardiogram Minor: Risk factors, >38°C, vascular or immunologic phenomena, echocardiogram or culture evidence that does not meet major criteria

Patient develops endocarditis 3 weeks after receiving a prosthetic heart valve. What organism is suspected?	*S aureus* or *S epidermidis*
Patient develops endocarditis in a native valve after having a dental cleaning	*S viridans*
IV drug use with JVD and a holosystolic murmur at the left sternal border. Treatment?	Treat existing heart failure, and replace the tricuspid valve
Evaluation of a pulsatile abdominal mass and bruit	Abdominal ultrasound and CT (concern for abdominal aortic aneurysm)
Indications for surgical correction of abdominal aortic aneurysm	>5.5 cm, rapidly enlarging, symptomatic, or ruptured
Syncope with arm exercise	Subclavian steal syndrome
Protamine	Reverses the effects of heparin
Prothrombin time	The coagulation parameter affected by warfarin
Virchow triad	Stasis, hypercoagulability, endothelial damage
Syncope after wearing a tie	Carotid sinus syndrome
Figure 3 sign on CXR	Aortic coarctation
Diagnostic test for pulmonary embolism	CT pulmonary angiogram

DERMATOLOGY

"Stuck-on" waxy appearance	Seborrheic keratosis
Erythematous plaques with silvery scales	Psoriasis
Most common malignant skin cancer. The lesion is a pearly nodule with superficial telangiectasias.	Basal cell carcinoma
Honey-crusted lesions	Impetigo
Febrile patient with history of diabetes presents with a red, swollen, painful lower extremity	Cellulitis
⊕ Nikolsky sign, flaccid bullae. Treatment?	Pemphigus vulgaris; high-dose systemic steroids + immunomodulator therapy
⊖ Nikolsky sign, tense bullae. Treatment?	Bullous pemphigoid; topical corticosteroids
Obese patient presents with hyperpigmented, velvety patches on back of neck	Acanthosis nigricans; check fasting blood glucose to rule out diabetes
Dermatomal distribution of crusted vesicles	Herpes zoster (shingles) due to reactivation of the varicella zoster virus
Violaceous, flat-topped, pruritic, polygonal papules or plaques	Lichen planus
Irislike target lesions	Erythema multiforme
Lesion occurring in a geometric pattern in areas where skin comes into contact with clothing or jewelry	Contact dermatitis

Presents with one large patch and many smaller ones in a treelike distribution	Pityriasis rosea
Flat, often hypopigmented lesions on the chest and back. KOH prep has a "spaghetti-and-meatballs" appearance	Tinea (pityriasis) versicolor
Five characteristics of a nevus suggestive of melanoma	Asymmetry, border irregularity, color variation, large diameter, clinical evolution (ABCDE)
Premalignant lesion caused by sun exposure that can lead to SCC	Actinic keratosis
Widespread pruritic lesions at various rash stages	Varicella (chicken pox)
"Cradle cap." Treatment?	Seborrheic dermatitis Treat conservatively with bathing and moisturizing agents
Associated with *Propionibacterium acnes* and changes in androgen levels	Acne vulgaris
Most effective treatment for severe acne. Adverse effects?	Oral isotretinoin; teratogen and elevated LFTs; requires monthly blood tests and two forms of contraception for women
Painful, recurrent vesicular eruption of mucocutaneous surfaces	Herpes simplex
Inflammation and epithelial thinning of the anogenital area, predominantly in postmenopausal women	Lichen sclerosus
The second most common skin cancer. Erythematous ulcerated nodule with erosion or ulceration on sun-damaged skin.	Squamous cell carcinoma
Name the organism: Lesions along draining lymphatics in a gardener	*Sporothrix schenckii*

ENDOCRINOLOGY

Most common cause of hypothyroidism	Hashimoto thyroiditis
Lab findings in Hashimoto thyroiditis	High TSH, low T_4, antibodies to thyroid peroxidase or to thyroglobulin
Exophthalmos, pretibial myxedema, and ↓TSH	Graves disease
Most common cause of Cushing syndrome	Iatrogenic corticosteroid administration; the second most common cause is Cushing disease
Post-thyroidectomy patient presents with signs of hypocalcemia and hyperphosphatemia	Hypoparathyroidism (iatrogenic)
"Stones, bones, groans, psychiatric overtones"	Signs and symptoms of hypercalcemia (kidney stones, bone disease, gastrointestinal symptoms, alterations in mentation)
Hypertension, hypokalemia, and metabolic alkalosis	Primary hyperaldosteronism (caused by Conn's syndrome or bilateral adrenal hyperplasia)
Patient presents with tachycardia, wild swings in BP, headache, diaphoresis, altered mental status, and a sense of panic	Pheochromocytoma
Which should be used first in treating pheochromocytoma, α- or β-antagonists?	α-antagonists (phenoxybenzamine)

Patient with history of lithium use presents with copious amounts of dilute urine	Nephrogenic DI
Treatment of central DI	DDAVP
Postoperative patient with significant pain presents with hyponatremia and normal volume status	SIADH due to stress
Antihyperglycemic agent associated with lactic acidosis	Metformin
Patient presents with weakness, nausea, vomiting, weight loss, and new skin hyperpigmentation. Lab results show hyponatremia and hyperkalemia. Treatment?	Primary adrenal insufficiency (Addison disease); treat with glucocorticoids, mineralocorticoids, and IV fluids
Treatment of DKA	Fluids, insulin, and electrolyte repletion (chiefly K^+)
Bone pain, hearing loss, ↑ alkaline phosphatase	Paget disease
↑ IGF-1	Acromegaly
Galactorrhea, amenorrhea, bitemporal hemianopia	Prolactinoma
↑ serum 17-hydroxyprogesterone	Congenital adrenal hyperplasia (21-hydroxylase deficiency)
Pancreas, pituitary, parathyroid tumors	MEN type 1

EPIDEMIOLOGY

Chronic diseases such as systemic lupus erythematosus—higher prevalence or incidence?	Higher prevalence
Epidemics such as influenza—higher prevalence or incidence?	Higher incidence
What is the difference between incidence and prevalence?	Prevalence: percentage of cases of disease in a population at one point in time Incidence: percentage of new cases of disease that develop over a given period among the total population at risk (prevalence = incidence × duration)
Describe a test that consistently gives identical results, but the results are wrong	High reliability (precision), low validity (accuracy)
The proportion of people who have the disease and test ⊕ is the _____	Sensitivity
Sensitive tests have few false negatives and are used to rule _____ a disease	Out
PPD reactivity is used as a screening test because most people with TB (except those who are anergic) will have a ⊕ PPD highly sensitive or specific?	Highly sensitive for TB

Odds ratio?	In cohort studies, the odds of developing the disease in the exposed group divided by the odds of developing the disease in the nonexposed group In case-control studies, the odds that the cases were exposed divided by the odds that the controls were exposed In cross-sectional studies, the odds that the exposed group has the disease divided by the odds that the nonexposed group has the disease
Attributable risk?	The difference in risk in the exposed and unexposed groups (ie, the risk that is attributable to the exposure)
Relative risk?	Incidence in the exposed group divided by the incidence in the nonexposed group
Hypothetical study found an association between ASA intake and risk for heart disease. How do you interpret an RR of 15?	In patients who took ASA, the risk for heart disease was 15 times that of patients who did not take ASA
Cross-sectional survey—incidence or prevalence?	Prevalence
Cohort study—incidence or prevalence?	Incidence and prevalence
Case-control study—incidence or prevalence?	Neither
Difference between a cohort and a case-control study	Cohort divides groups by an exposure and looks for development of disease Case-control divides groups by a disease and assigns controls, and then goes back and looks for exposures
How do you interpret the following 95% CI for an RR of 0.582: 95% CI 0.502, 0.673?	Data are consistent with RRs ranging from 0.502 to 0.673 with 95% confidence (ie, we are confident that, 95 out of 100 times, the true RR will be between 0.502 and 0.673)
Bias introduced into a study when a clinician is aware of the patient's treatment type	Observational bias
Bias introduced when screening detects a disease earlier and thus lengthens the time from diagnosis to death, but does not improve survival	Lead-time bias
If you want to know if geographic location affects infant mortality rate but most variation in infant mortality is predicted by socioeconomic status, then socioeconomic status is a _____	Confounding variable
The percentage of cases within 1 SD of the mean? 2 SDs? 3 SDs?	68%, 95.4%, 99.7%
Most common cancer in men and most common cause of death from cancer in men	Prostate cancer is the most common cancer in men, but lung cancer causes more deaths
Birth rate?	Number of live births per 1000 population in 1 year
Mortality rate?	Number of deaths per 1000 population in 1 year
Neonatal mortality rate?	Number of deaths from birth to 28 days per 1000 live births in 1 year
Infant mortality rate?	Number of deaths from birth to 1 year of age per 1000 live births (neonatal + postnatal mortality) in 1 year
Maternal mortality rate?	Number of deaths during pregnancy to 90 days postpartum per 100,000 live births in 1 year

HEALTH SYSTEMS SCIENCE

When is hospice care indicated?	When prognosis is <6 months or life prolonging treatment is no longer beneficial
Interview strategy in patient with alcoholism when patient is: 1. Not considering quitting. 2. Thinking of quitting. 3. Ready to quit, but has taken no action. 4. Demonstrated motivation to quit through small steps/actions. 5. Recently implemented plan to quit. 6. Automatically implements behavioral changes to remain sober	Patient stage → interview strategy 1. Precontemplation (not ready to change) → Discuss risks and consequences 2. Contemplation (thinking of change) → encourage evaluation of pros and cons 3. Preparation (ready for change) → encourage small steps 4. Action (patient making change) → identify appropriate strategies and enlist social support</nl> 5. Maintenance (implemented change) → follow-up support, relapse prevention 6. Identification (behavior automatic) → praise changes
Most effective intervention to improve communication during patient transfers?	Checklists
What is a sentinel event?	Any event that results in death, serious physical harm or psychologic harm to a patient
Type of analysis used to find the reason for a sentinel event?	Root cause analysis
Involuntary psychiatric hospitalization can be undertaken for which three reasons?	The patient is a danger to self, a danger to others, or gravely disabled (unable to provide for basic needs)
Parent of Jehovah's Witness rejects emergency transfusion for their child. What should the clinician do?	Clinician not obliged to agree with parent and must provide treatment in the best interest of the child (beneficence)
Patient refuses lifesaving treatment. What is the next step?	Discuss the reason behind the patient's decision before accepting it.
True or false: Once patients sign a statement giving consent, they must continue treatment	False; patients may change their minds at any time Exceptions to the requirement of informed consent include emergency situations and patients without decision-making capacity
Involuntary commitment or isolation for medical treatment may be undertaken for what reason?	When treatment noncompliance represents a serious danger to public health (eg, active TB)
When is a minor considered legally emancipated (doesn't require parental consent)?	In general, a minor is emancipated if he/she is: married, in armed services, parent of a child that they support, financially independent and has obtained legal emancipation
15-year-old pregnant girl requires hospitalization for preeclampsia. Is parental consent required?	No, parental consent is not necessary for the medical treatment of pregnant minors
Mother refuses to allow her child to be vaccinated	Parent has the right to refuse treatment for his or her child as long as it does not pose a serious threat to child's well-being
8-year-old child is in a serious accident and requires emergent transfusion, but her parents are not present	Treat immediately; consent is implied in emergency situations
15-year-old girl seeking treatment for an STI asks that her parents not be told about her condition	Minors may consent to care for STIs without parental consent or knowledge

10-year-old child presents in status epilepticus, but her parents refuse treatment on religious grounds	Treat because the disease represents an immediate threat to the child's life
In a non-emergency, parents refuse life-saving treatment for child. What is the next step?	Obtain a court order before treatment
True or false: It is more difficult to justify the withdrawal of care (e.g., mechanical ventilation) than to have withheld the treatment in the first place	False; withdrawing nonbeneficial treatment (eg, mechanical ventilation) or treatment a patient no longer wants is ethically equivalent to withholding care
When can a physician refuse to continue treating a patient on the grounds of futility?	When there is no rationale for treatment, maximal intervention is failing, a given intervention has already failed, and treatment will not achieve the goals of care
Patient requests to undergo complementary medical treatment (acupuncture). What is the doctor's next step?	Understand the reasons for the patient's request; be ready to discuss risks and benefits, and be open to
Son asks that his mother not be told about her recently discovered cancer	Physician can withhold information from the patient only in the rare case of therapeutic privilege or if patient requests not to be told
In what setting is bad news best delivered?	Always deliver bad news face-to-face Follow the **SPIKES** framework (ensure appropriate **S**etting, assess patient's **P**erception, **I**nvite questions and assess how much information they know and would like, impart **K**nowledge, acknowledge **E**motions, **S**trategize next step when ready)
Patient's family asks you not to provide information about a serious diagnosis to patient. What is the next step?	Do not deliver the diagnosis initially First, ask the patient whether she would like important health information communicated to her, and respect the decision if she prefers not to know about it
Conditions in which confidentiality must be overridden	Real threat of harm to third parties Suicidal intentions Certain contagious diseases Elder and child abuse
Doctor refers patient for an MRI to a facility that doctor owns	Conflict of interest
What kind of gift can you accept from a pharmaceutical representative?	Nonmonetary, low value gifts that directly benefit the patient, eg, drug samples can be considered

GASTROINTESTINAL

Patient presents with sudden onset of severe, diffuse abdominal pain. Exam reveals peritoneal signs, and x-ray of the abdomen reveals free air under the diaphragm. Management?	Emergent laparotomy to repair a perforated viscus
Most likely cause of acute lower GI bleeding in patients >40 years of age	Diverticulosis
Diagnostic modality used when ultrasonography is equivocal for cholecystitis	HIDA scan
Risk factors for cholelithiasis	Fat, female, fertile, forty, flatulent

Inspiratory arrest during palpation of the RUQ	Murphy sign, seen in acute cholecystitis
Most common cause of SBO in patients with no history of abdominal surgery	Hernia (also concerning for cancer)
Most common cause of SBO in patients with a history of abdominal surgery	Adhesions
Identify key organisms causing diarrhea:	
- Most common bacterial organism	*Campylobacter*
- Recent antibiotic use	*Clostridium difficile*
- Camping	*Giardia*
- Traveler's diarrhea	Enterotoxigenic *Escherichia*
- Church picnics/mayonnaise	*S aureus*
- Uncooked hamburgers	*E coli* O157:H7
- Fried rice	*Bacillus cereus*
- Poultry/eggs	*Salmonella*
- Raw seafood	*Vibrio*, HAV
- AIDS	*Isospora, Cryptosporidium, Mycobacterium avium* complex
- Pseudoappendicitis	*Yersinia, Campylobacter*
25-year-old man presents with pain and watery diarrhea after meals. Exam shows fistulas between the bowel and skin and nodular lesions on his tibias	Crohn disease
Inflammatory disease of the colon with ↑ risk for colon cancer	Ulcerative colitis (greater risk than Crohn)
Extraintestinal manifestations of IBD	Uveitis, ankylosing spondylitis, pyoderma gangrenosum, erythema nodosum, primary sclerosing cholangitis
Medical treatment for IBD	5-ASA agents and steroids during acute exacerbations
30-year-old man with ulcerative colitis presents with fatigue, jaundice, and pruritus	Primary sclerosing cholangitis
Difference between Mallory-Weiss and Boerhaave tears	Mallory-Weiss: superficial tear in the esophageal mucosa Boerhaave: full-thickness esophageal rupture
Charcot triad	RUQ pain, jaundice, and fever/chills
Reynolds pentad	Charcot triad plus shock and altered mental status
Medical treatment for hepatic encephalopathy	↓ protein intake, lactulose, rifaximin
The first step in management of a patient with an acute GI bleeding episode	Manage ABCs
4-year-old child presents with oliguria, petechiae, and jaundice following an illness with bloody diarrhea. Most likely diagnosis and cause?	HUS caused by *E coli* O157:H7
Treatment after occupational exposure to HBV	If nonimmune, provide HBV immunoglobulin and initiate HBV vaccination series

Classic causes of drug-induced hepatitis	TB medications (isoniazid, rifampin, pyrazinamide), acetaminophen, and tetracycline
40-year-old obese woman with elevated alkaline phosphatase, elevated bilirubin, pruritus, dark urine, and clay-colored stools	Biliary tract obstruction
Hernia with highest risk for incarceration—indirect, direct, or femoral?	Femoral hernia
Severe abdominal pain out of proportion to the exam	Mesenteric ischemia
Diagnosis of ileus	Abdominal radiographs (could also perform CT scan)
50-year-old man with history of alcohol overuse presents with epigastric pain that radiates to the back and is relieved by sitting forward. Management?	Confirm diagnosis of acute pancreatitis with ↑ amylase and lipase (± CT abdomen pelvis) Make the patient NPO, and give IV fluids, O_2, analgesia, and "tincture of time"
Colon cancer region based on symptoms: Anemia from chronic disease, occult blood loss, vague abdominal pain Obstructive symptoms, change in bowel movements	Right sided: rare to have an obstruction Left-sided: "apple core" lesion
Presents with watery diarrhea, dehydration, muscle weakness, and flushing	VIPoma (replace fluids and electrolytes, may need to surgically resect tumor, or use octreotide)
Presents with palpable, nontender gallbladder	Courvoisier sign (suggests pancreatic cancer)
24-year-old man presents with soft white plaques on his tongue and the back of his throat. Diagnosis? Work-up? Treatment?	Candidal thrush; workup should include an HIV test; treat with nystatin oral suspension
Name the organism: ■ Sheepherders with liver cysts ■ Perianal itching	 *Echinococcus granulosus* *Enterobius vermicularis*
Causes of pill esophagitis	Bisphosphonates, Tetracyclines, NSAIDs, ascorbic acid
Type of esophageal cancer in the upper third and lower third?	Upper third—SCC Lower third—adenocarcinoma
Zollinger Ellison syndrome	Gastrin secreting neuroendocrine tumor; Treat with high dose of PPIs
Indications for bariatric surgery	BMI >40; BMI 35–39.9 with at least one comorbidity (eg, OSA, DM, HTN); BMI 30–34.9 with uncontrolled type 2 DM or metabolic syndrome
Diagnosis of celiac disease	IgA anti-transglutaminase antibody, anti-endomysial antibody
Presentation of acute mesenteric ischemia?	Acute abdominal pain with blood per rectum
Management of acute GI bleeding	ABCs, stabilize hemodynamics
Diagnosis of spontaneous bacterial peritonitis?	Ascitic fluid PMNs >250
Causes of acute hepatitis causing LFTs >1000 U/L?	Drug-induced hepatitis, viral hepatitis, ischemic hepatitis

HEMATOLOGY

Five causes of microcytic anemia	**IRON LAST—IRON** deficiency, **L**ead poisoning, **A**nemia of chronic disease, **S**ideroblastic anemia, **T**halassemia
Elderly man with hypochromic microcytic anemia. Diagnostic test?	Suspect colorectal cancer, sigmoidoscopy/colonoscopy
Precipitants of hemolytic crisis in G6PD deficiency	**Sell fava beans in INDIA**—Sulfa drugs, **fava beans,** **I**nfections, **N**itrofurantoin, **D**apsone, **I**soniazid, **A**ntimalarials
Most common inherited cause of hypercoagulability	Factor V Leiden mutation
Most common inherited bleeding disorder	von Willebrand disease
Most common inherited hemolytic anemia	Hereditary spherocytosis
Diagnostic test for hereditary spherocytosis	Osmotic fragility test
How do you differentiate between AIHA and hereditary spherocytosis?	Spherocytes, ⊕ ve osmotic fragility tests, but only AIHA has ⊕ direct Coombs test
Pure RBC aplasia	Diamond-Blackfan anemia
Anemia associated with absent radii and thumbs, diffuse hyperpigmentation, café au lait spots, microcephaly, and pancytopenia	Fanconi anemia
Medications and viruses causing Aplastic anemia	Chloramphenicol, sulfonamides, radiation, HIV, chemotherapeutic agents, hepatitis, parvovirus B19, EBV
How to distinguish polycythemia vera from secondary polycythemia?	Both have ↑ hematocrit and RBC mass, but polycythemia vera should have normal O_2 saturation and low erythropoietin levels
TTP pentad	**LMNOP—L**ow platelet count (thrombocytopenia), **M**icroangiopathic hemolytic anemia, **N**eurologic changes, "**O**bsolete" renal function, **P**yrexia
Treatment for TTP	Emergent large-volume plasmapheresis, corticosteroids, antiplatelet drugs
HUS triad	Anemia (microangiopathic hemolytic anemia), thrombocytopenia, and acute renal failure
ITP treatment?	Children: Usually resolves spontaneously Adults: May require IVIG and/or corticosteroids
Diagnostic tests in DIC?	Fibrin split products and D-dimer are ↑; platelets, fibrinogen, and hematocrit are ↓
8-year-old boy presents with hemarthrosis and ↑ PTT with normal PT and bleeding time. Diagnosis? Treatment?	Hemophilia A or B; consider desmopressin (for hemophilia A) or factor VIII or IX supplements
14-year-old girl presents with prolonged bleeding after dental surgery and with menses, normal PT, normal or ↑ PTT, and ↑ bleeding time. Diagnosis? Treatment?	von Willebrand disease; treat with desmopressin, FFP, or cryoprecipitate

Findings in multiple myeloma	Monoclonal gammopathy, Bence Jones proteinuria, and "punched out" lesions on radiographs of the skull and long bones
Reed-Sternberg cells	Hodgkin lymphoma
Microcytic anemia with ↓ serum iron, ↓ ferritin, and ↑ TIBC	Iron-deficiency anemia
Microcytic anemia with ↓ serum iron, ↓ TIBC, and normal or ↑ferritin	Anemia of chronic disease
80-year-old man presents with fatigue, lymphadenopathy, splenomegaly, and isolated lymphocytosis. Diagnosis?	CLL
Causes of ↓ hemoglobin and ↑ mean corpuscular volume?	Vitamin B$_{12}$ deficiency (pernicious anemia, vegetarian diet, Crohn/GI disorders) or folate deficiency (alcohol use disorder)
Late, life-threatening complication of CML	Blast crisis (fever, bone pain, splenomegaly, pancytopenia)
Auer rods on blood smear	AML
AML subtype associated with DIC? Treatment?	APL (M3); All-trans retinoic acid
Electrolyte changes in tumor lysis syndrome	↓ Ca^{2+}, ↓ K^{+}, ↓ phosphate, ↓ uric acid
CML cytogenetics	t(9,22)
CML treatment?	BCR-ABL tyrosine kinase inhibitors—imatinib
Neutropenic fever. Diagnosis? Treatment?	ANC <1500 cells/mm^3; broad-spectrum antibiotics
Virus associated with aplastic anemia in patients with sickle cell anemia	Parvovirus B19
Treatment of bone crisis in sickle cell anemia?	O$_2$, analgesia, hydration, and, if severe, transfusion
Significant cause of morbidity in thalassemia patients. Treatment?	Iron overload; treat with deferoxamine
Aplastic crisis in sickle cell disease	Parvovirus B19

MUSCULOSKELETAL

Fractures that occur during fall onto an outstretched hand	Colles fracture, Smith fracture, scaphoid fracture
Most common hip dislocation. Clinical presentation? Complication?	Posterior hip dislocation; painful hip in a position of flexion, internal rotation and adduction; sciatic nerve injury
Knee injury due to noncontact twisting mechanism or direct impact on a hyperextended knee	Anterior cruciate ligament injury
Pain at base of posterior foot reproducible with compression of the calcaneum	Calcaneal stress fracture
Pain in the heel and sole of foot that worsens on prolonged weight bearing	Plantar fasciitis
Paresthesia in the sole of the foot and pain upon foot dorsiflexion and eversion	Tarsal tunnel syndrome

X-ray findings in bone tumor associated with Li-Fraumeni syndrome and familial retinoblastoma	Osteosarcoma; medullary and cortical bone destruction with sunburst appearance and Codman triangle
Septic arthritis synovial fluid findings and empiric antibiotic treatment.	WBC count >50,000/mm³, PMN >90% and ⊕ Gram stain; ceftriaxone and vancomycin until culture test results
Adult with fever and localized bone pain with MRI showing bone marrow inflammation and soft tissue infection	Osteomyelitis
Joint pain and stiffness that worsen over the course of the day and are relieved by rest	Osteoarthritis
Joints in the hand affected in rheumatoid arthritis	MCP and PIP joints; DIP joints are spared
Arthritis, conjunctivitis, and urethritis in young adults. Associated organisms?	Reactive arthritis; most commonly associated with *Chlamydia*, also consider *Campylobacter, Shigella, Salmonella,* and *Ureaplasma*
Young woman presents with fever, malaise, malar rash and arthritis. Associated antibodies?	Systemic lupus erythematosus; ⊕ ANA, anti-dsDNA and anti-Smith antibodies
Shoulder pain with weak abduction and external rotation of the humerus	Rotator cuff tear
55-year-old man has sudden, excruciating first MTP joint pain after a night of drinking red wine. Diagnosis, work-up, and chronic treatment?	Gout; needle-shaped, negatively birefringent crystals are seen on joint fluid aspirate; chronic treatment with allopurinol or probenecid
Rhomboid-shaped, positively birefringent crystals on joint fluid aspirate	Calcium pyrophosphate deposition disease
Name the organism:	
▪ Raw pork and skeletal muscle cysts	*Trichinella spiralis*
▪ Osteomyelitis from a foot wound puncture	*Pseudomonas*
▪ Osteomyelitis in a sickle cell patient	*Salmonella*

NEUROLOGY

Unilateral, severe periorbital headache with tearing and conjunctival erythema	Cluster headache
Prophylactic treatment for migraine	Antihypertensives, antidepressants, anticonvulsants, dietary changes
Treatment of stroke if presentation within 3–4.5 hours?	Thrombolytics (tissue plasminogen activators tPA)
Most common pituitary tumor. Treatment?	Dopamine agonists (eg, bromocriptine, cabergoline)
55-year-old patient presents with acute "broken speech."	
▪ Type of aphasia?	Broca aphasia
▪ Lobe?	Frontal lobe
▪ Vascular distribution?	Left MCA distribution
Most common cause of SAH	Trauma (second most common is berry aneurysm)
CSF findings with SAH	↑ ICP, RBCs, xanthochromia
Lens-shaped hypedensity on CT head; patient has a lucid interval	Epidural hematoma; middle meningeal artery

Crescent-shaped hyperdensity on CT that does not cross the midline	Subdural hematoma—bridging veins torn (seen in elderly and young children)
Albuminocytologic dissociation	Guillain-Barré syndrome (↑ protein in CSF without a significant increase in cell count)
Most common cause of brain neoplasm	Metastases, primary neoplasms are much less common
Most common primary sources of metastases to the brain	Lung, breast, skin (melanoma), kidney, GI tract
Most common cause of seizures in children (2–10 years of age)	Infection, febrile seizures, trauma, idiopathic
Most common cause of seizures in young adults (18–35 years of age)	Trauma, alcohol withdrawal, brain tumor
Classic EEG finding of absence seizures?	3-per-second spike and wave discharges
First-line medication for status epilepticus	IV benzodiazepine
Hearing loss in presbycusis	High frequency
Ring enhancing lesions in patients with AIDS	Toxoplasmosis, CNS lymphoma
Differences between myasthenia gravis and Lambert-Eaton myasthenic syndrome on nerve stimulation	Decremental response in MG, Incremental response in LEMS
Symptoms seen in normal pressure hydrocephalus?	Gait ataxia (wobbly), urinary incontinence (wet), dementia (wacky)
Risk factors for intracranial hypertension?	Obesity, Tetracycline, growth hormone, excess vitamin A
Wernicke encephalopathy	Confusion, ophthalmoplegia, ataxia caused by a deficiency of thiamine (B$_1$)
Most common causes of dementia	Alzheimer disease and vascular
Combined UMN and LMN disorder	ALS
Rigidity and stiffness with unilateral resting tremor and masked facies	Parkinson disease
Treatment for Parkinson disease	Levodopa/carbidopa
Treatment for Guillain-Barré syndrome	IVIG or plasmapheresis; avoid steroids
Rigidity and stiffness that progress to choreiform movements, accompanied by moodiness and altered behavior	Huntington disease; autosomal dominant
Port-wine stain in the V$_1$ distribution as well as with intellectual disability, seizures, and ipsilateral leptomeningeal angioma	Sturge-Weber syndrome; treat symptomatically; possible focal cerebral resection of affected lobe
Multiple café-au-lait spots on skin	Neurofibromatosis type 1
Hyperphagia, hypersexuality, hyperorality, and hyperdocility	Klüver-Bucy syndrome (amygdala)
Name the organism:	
▪ Meningitis in adults	*Neisseria meningitidis*
▪ Meningitis in elderly	*Streptococcus pneumoniae*
▪ Meningoencephalitis in AIDS patients	*Cryptococcus neoformans*
Causes of ring-enhancing brain lesions	Abscess, toxoplasmosis, metastasis, lymphoma, AIDS, neurocysticercosis

Causes of meningitis in neonates. Treatment?	GBS, *E coli*, Listeria; treat with ampicillin + cefotaxime or gentamicin
Causes of meningitis in infants. Treatment?	*S pneumoniae, N meningitidis, H influenzae* type B; treat with vancomycin + cefotaxime
What must always be done before LP?	Check for ↑ ICP; look for papilledema
CSF findings:	
■ Low glucose, PMN predominance	Bacterial meningitis
■ Normal glucose, lymphocytic predominance	Aseptic (viral) meningitis
■ Numerous RBCs in serial CSF samples	SAH
■ Gamma globulins	MS

OBSTETRICS

Screening time for GBS. Intrapartum prophylaxis administered if ⊕ GBS	Rectovaginal swab at 36–38 weeks; IV penicillin
Quadruple screening findings in Trisomy 21 gestation	↓ MSAFP, ↓ estriol, ↑ inhibin A, ↑ β-hCG
Intellectual disability, midfacial hypoplasia, smooth philtrum, cardiac defects	Fetal alcohol syndrome
Fetal growth restriction, microcephaly, cleft palate, fingernail hypoplasia, coarse hair	Fetal hydantoin syndrome
Chorioretinitis, hydrocephalus, diffuse intracranial calcifications, ring enhancing lesions in newborn	Congenital toxoplasmosis
Petechial rash, sensorineural hearing loss, periventricular calcifications in newborn	Congenital CMV infection
Uterine bleeding at <20 weeks. No products expelled. Open cervical os	Inevitable abortion
Uterine bleeding at <20 weeks. No products expelled. Closed cervical os	Threatened abortion
Best initial test for gestational diabetes mellitus	Routine screening with a 1-hour 50g glucose challenge test at 24–28 weeks
Severe preeclampsia, hemolytic anemia, elevated liver enzymes, low platelets	HELLP syndrome
RUQ pain, elevated liver enzymes, low platelets, profound hypoglycemia	Acute fatty liver in pregnancy
Treatment of asymptomatic bacteriuria	3–7 days of nitrofurantoin or amoxicillin-clavulanate
Painful vaginal bleeding, uterine hypertonicity, fetal distress	Placental abruption
Painless vaginal bleeding after rupture of membranes, fetal bradycardia	Vasa previa
C-section, fever, lower abdominal pain, foul smelling lochia. Treatment?	Postpartum endometritis IV clindamycin ⊕ gentamicin
Contraindication to breastfeeding	HIV infection, active herpes simplex on breast, active substance use, galactosemia

GYNECOLOGY

Features of Turner syndrome?	Streak gonads, shield chest, amenorrhea, webbed neck, aortic coarctation, bicuspid aortic valve
Most common cause of amenorrhea	Pregnancy
Use of OCPs decreases risk of which cancers?	Endometrial, ovarian
Cause of amenorrhea with normal prolactin, no response to estrogen-progesterone challenge, and a history of D&C	Asherman syndrome
Therapy for polycystic ovarian syndrome	Weight loss and OCPs
Medication used to induce ovulation	Clomiphene
Diagnostic step required in a postmenopausal woman who presents with vaginal bleeding	Endometrial biopsy for suspected endometrial carcinoma
Indications for medical treatment of ectopic pregnancy in a stable patient	Unruptured ectopic pregnancy of <35 cm at <6 weeks gestation
Medical treatment for endometriosis	OCPs, danazol, GnRH agonists
Laparoscopic findings in endometriosis	Powder burns, "chocolate cysts"
Most common location for an ectopic pregnancy	Ampulla of the fallopian tube
Natural history of a leiomyoma	Regresses after menopause
Treatment for bacterial vaginosis	Oral metronidazole
Diagnostic step for breast mass in premenopausal and postmenopausal, >30 years of age women?	Premenopausal and <30 years of age: Ultrasound Postmenopausal and >30 years of age: Mammogram
Most common cause of bloody nipple discharge	Intraductal papilloma, mammary duct ectasia
Unopposed estrogen is contraindicated in which cancers?	Endometrial or estrogen receptor ⊕ breast cancer
Side effects of tamoxifen?	Hot flashes, endometrial cancer, venous thromboembolism
Patient presents with recent PID with RUQ pain	Consider Fitz-Hugh–Curtis syndrome
Screening for women with a strong family history of ovarian cancer	CA-125 and transvaginal ultrasonography
Lab values suggestive of menopause	↑ serum FSH
Two consecutive findings of ASCUS on Pap smear. Next step?	Colposcopy and endocervical curettage
Breast cancer type that ↑ future risk for invasive carcinoma in both breasts	Lobular carcinoma in situ

PEDIATRICS

Nontender abdominal mass associated with ↑ urinary VMA and HVA	Neuroblastoma
Most common type of TEF? How does it present?	Esophageal atresia with distal TEF (85%); inability to pass NG tube

Beckwith-Weidemann syndrome presentation and associations	Macrosomia, omphalocele, macroglossia, hemihypertrophy Wilms tumor, hepatoblastoma, neuroblastoma, adrenal tumors
Contraindications to vaccination	Life-threatening egg allergies (needs close observation for MMR and influenza) Encephalopathy within 7 days of prior pertussis vaccination or uncontrolled seizure disorder Personal history of intussusception (rotavirus vaccination) Pregnant/immunocompromised patients (avoid live vaccinations) Weight <2 kg (4 lb, 6 oz) for hepatitis B vaccine in newborn
Tests to rule out abusive head trauma	Ophthalmologic exam, CT, and MRI
Neonate has meconium ileus	Cystic fibrosis (Hirschsprung disease is associated with failure to pass meconium for 48 hours)
Bilious emesis within hours after the first feeding	Duodenal atresia
2-month-old infant presents with nonbilious projectile emesis. Diagnosis? Next steps in management?	Pyloric stenosis Hydrate and correct metabolic abnormalities; then correct pyloric stenosis with pyloromyotomy
Most common primary immunodeficiency	Selective IgA deficiency
Infant has high fever and onset of rash as fever breaks. What is he at risk for?	Febrile seizures (caused by roseola infantum)
What is the immunodeficiency?	
▪ Child has recurrent, severe catalase positive bacterial infections. Nitroblue tetrazolium test fails to turn blue	Chronic granulomatous disease
▪ Child has eczema, thrombocytopenia, and high levels of IgA and IgE	Wiskott-Aldrich syndrome (**WIPE: W**iskott-Aldrich, **I**nfections, **P**urpura, **E**czema)
▪ 6-month-old boy has life-threatening *Pseudomonas* infection	Bruton's X-linked agammaglobulinemia
Acute-phase treatment for Kawasaki disease	High-dose ASA for inflammation and fever IVIG to prevent coronary artery aneurysm
Treatment for mild and severe unconjugated hyperbilirubinemia	Phototherapy (mild) or exchange transfusion (severe) Do not use phototherapy for conjugated hyperbilirubinemia
Sudden onset of altered mental status, emesis, and liver dysfunction after ASA intake	Reye syndrome
Child has loss of red light reflex (white pupil). Diagnosis? Risk for which cancer is ↑?	Suspect retinoblastoma Osteosarcoma
Vaccinations at a 6-month well-child visit	HBV, DTaP, Hib, IPV, PCV-13, rotavirus, influenza
Secondary sexual maturation in girls <8 years or boys <9 years	Precocious puberty
Infection of small airways with epidemics in winter and spring	RSV bronchiolitis
Cause of neonatal RDS	Surfactant deficiency
Red "currant-jelly" stools, colicky abdominal pain, bilious vomiting, and a sausage-shaped mass in the RUQ	Intussusception

Congenital heart disease that causes secondary hypertension. Findings on physical exam?	Coarctation of the aorta Pulse and blood pressure discrepancy between upper and lower extremities
First-line treatment for otitis media	Amoxicillin
Most common pathogen causing croup	Parainfluenza virus type 1
Homeless child is small for his age and has peeling skin and a swollen belly	Kwashiorkor (protein malnutrition)
Defect in an X-linked syndrome with intellectual disability, gout, self-mutilation, and choreoathetosis	Lesch-Nyhan syndrome (purine salvage problem with HGPRTase deficiency)
Newborn girl has continuous "machinery murmur." What drug would you give?	PDA; give indomethacin to close the PDA
Newborn girl with a posterior neck mass and swelling of the hands	Turner syndrome
Young child presents with proximal muscle weakness, waddling gait, and pronounced calf muscles	Duchenne muscular dystrophy
First-born female who was born in breech position is found to have asymmetric gluteal folds on newborn exam. Diagnosis? Treatment?	Developmental dysplasia of the hip; <6 months Pavlik harness to maintain hips in flexion and abduction
11-year-old obese African-American boy presents with sudden onset of limp. Diagnosis? Workup?	Slipped capital femoral epiphysis; AP and frog-leg lateral x-rays
Active 13-year-old boy has anterior knee pain. Diagnosis?	Osgood-Schlatter disease

PSYCHIATRY

First-line pharmacotherapy for depression	SSRIs
Galactorrhea, impotence, menstrual dysfunction, and ↓ libido	Adverse effects of dopamine antagonists
17-year-old girl has left arm paralysis after her boyfriend dies in a car crash. No organic medical cause is found	Conversion disorder
Name the defense mechanism:	
■ Mother who is angry at her husband, yells at her child	Displacement
■ Girl who is upset with her best friend acts overly kind	Reaction formation
■ Hospitalized 10-year-old begins to wet his bed	Regression
Life-threatening muscle rigidity, high fever, autonomic instability, confusion, and elevated creatine phosphokinase	Neuroleptic malignant syndrome
Amenorrhea, low body weight (BMI <18.5), bradycardia, and distorted body image in a young woman	Anorexia
35-year-old man has recurrent episodes of palpitations, diaphoresis, and intense fear	Panic disorder
Most serious side effect of clozapine	Agranulocytosis
21-year-old man has 3 months of social withdrawal, worsening grades, flattened affect, and concrete thinking	Schizophreniform disorder (diagnosis of schizophrenia requires ≥6 months of symptoms)

Key side effects of atypical antipsychotics	Weight gain, glucose intolerance, QT-segment prolongation
Young man receives IV haloperidol and complains that his eyes are deviated sideways. Diagnosis? Treatment?	Acute dystonia (oculogyric crisis) Treat with benztropine or diphenhydramine
13-year-old boy has a history of theft, vandalism, and violence toward family pets	Conduct disorder; associated with antisocial personality disorder in adults
Previously healthy 6-month-old girl has ↓ head growth, truncal discoordination, and ↓ social interaction	Rett disorder; regression and loss of milestones is common. Stereotypical hand wringing
Patient has not slept for days, lost \$20,000 gambling, is agitated, and has pressured speech. Diagnosis? Treatment?	Acute mania Start an atypical antipsychotic and mood stabilizer (eg, lithium)
After a minor "fender bender," man wears a neck brace and requests permanent disability	Malingering
Health care worker presents with severe hypoglycemia. Blood analysis reveals no elevation in C-peptide	Factitious disorder
Patient spends most of his time acquiring cocaine despite losing his job and being threatened with legal charges	Substance use disorder
Violent patient has vertical and horizontal nystagmus	PCP intoxication
Woman who was abused as a child frequently feels outside of or detached from her body	Depersonalization disorder
Schizophrenic patient takes haloperidol for 1 year and develops uncontrollable tongue movements. Diagnosis? Treatment?	Tardive dyskinesia; ↓ or discontinue haloperidol, and consider another antipsychotic (eg, risperidone, clozapine)
Man with major depressive disorder is counseled to avoid tyramine-rich foods with his new medication. What class of medications is he taking?	MAO inhibitors

PULMONARY

Normalizing PCO$_2$ in a patient having an asthma exacerbation may indicate _____.	Fatigue and impending respiratory failure
Treatment for acute asthma exacerbation	β_2-agonists and corticosteroids
All adults and adolescents with asthma should get which medication long-term?	Inhaled corticosteroids regardless of severity
PFTs of restrictive pulmonary disease	Normal or ↑ FEV1/FVC, ↓ TLC
Honeycomb pattern on chest radiograph. Treatment?	Interstitial lung disease (AKA, diffuse parenchymal lung disease) Supportive care; antifibrotic agents may help
Treatment for acute COPD exacerbation	O$_2$ (if hypoxic), β_2-agonists (albuterol), muscarinic antagonist (ipratropium), corticosteroids, and ± antibiotics
Treatment for COPD exacerbation	O$_2$, bronchodilators, antibiotics, corticosteroids with taper, smoking cessation

Interventions that confer mortality benefit in COPD	Smoking cessation, long-term oxygen therapy, and lung volume reduction surgery (in some COPD patients)
Treatment for chronic COPD	Smoking cessation, home O_2, β_2-agonists (albuterol), anticholinergics (ipratropium), systemic or inhaled corticosteroids, flu and pneumococcal vaccines
Sarcoidosis	Dyspnea, bilateral hilar lymphadenopathy on CXR, noncaseating granulomas, ↑ ACE, and hypercalcemia
Sequelae of asbestos exposure	Pulmonary fibrosis, pleural plaques, bronchogenic carcinoma (mass in lung field), mesothelioma (pleural mass)
↑ risk for what infection with silicosis?	*Mycobacterium tuberculosis*
ARDS	Hypoxemia and pulmonary edema with normal PCWP
Causes of hypoxemia	Right-to-left shunt, hypoventilation, low inspired O_2 tension, diffusion defect, V/Q mismatch
An increase in plateau pressure represents reduced _______ of the lung	Compliance
Acute hypotension in ventilated patient may be due to (3 reasons)?	Tension pneumothorax, reduced venous return (secondary to high PEEP), or drugs (sedatives/opioids)
Classic chest radiographic findings for pulmonary edema	Cardiomegaly, prominent pulmonary vessels, Kerley B lines, "bat's wing" appearance of hilar shadows, and perivascular and peribronchial cuffing
Risk factors for DVT	Stasis, endothelial injury, and hypercoagulability (Virchow triad)
Acid-base disorder in PE	Respiratory alkalosis with hypoxia and ↓ $PaCO_2$
Chest radiography findings suggestive of PE	Westermark sign and Hampton hump (although most often normal)
Treatment for SVC syndrome	Radiation and endovascular stenting
NSCLC associated with hypercalcemia	SCC (ectopic PTHrP)
Lung cancer associated with SIADH	SCLC (ectopic ADH)
Lung cancer(s) associated with Lambert Eaton syndrome	SCLC
Lung cancer(s) highly related to cigarette exposure	SCLC, SCC
Characteristics favoring carcinoma in an isolated pulmonary nodule	Age >45–50 years Tobacco use Lesions new or larger in comparison to old x-rays Absence of calcification or irregular calcification Size >2 cm Irregular margins
Tests for latent TB	Tuberculin skin test or Interferon Gamma Release Assay
Management in patients with massive hemoptysis (>600 mL)	After securing airway and addressing breathing and circulation, the patient should undergo bronchoscopy to identify and treat bleeding

Criteria for exudative effusion	Pleural/serum protein >0.5, OR pleural/serum LDH >0.6
Causes of exudative effusion	Think of leaky capillaries (secondary to inflammation): malignancy, TB, bacterial or viral infection, PE with infarct, and pancreatitis
Causes of transudative effusion	Think of intact capillaries and hydrostatic pressure: HF, liver or kidney disease, and protein-losing enteropathy
Tall white man presents with acute shortness of breath. Diagnosis? Treatment?	Spontaneous pneumothorax Will regress spontaneously, but supplemental O_2 may be helpful
Treatment of tension pneumothorax	Immediate needle thoracostomy (over diagnostic) followed by chest tube placement
Snoring and daytime sleepiness raises suspicion for ____, which is diagnosed with _____ and initially treated with ______	OSA, nocturnal polysomnography, CPAP and weight loss
Brisk epistaxis continuing despite nasal packing may suggest a ____ source.	Posterior
Fever and hypotension 3 days after nasal packing for epistaxis may be due to?	Toxic shock syndrome
Most common cause of chronic cough are (name 3)?	Asthma, upper airway cough syndrome (postnasal drip), and gastroesophageal reflux disease
Most effective agent for the treatment of allergic rhinitis?	Glucocorticoid nasal spray
A patient has asthma, wheezing with aspirin/NSAIDS, and recurrent nasal discharge. What lesion does she have in her nasal cavities?	Nasal polyps Aspirin exacerbated respiratory disease presents with Samter triad (asthma, sinus disease with recurrent nasal polyps, and sensitivity to aspirin/NSAIDS)
Centor criteria for strep pharyngitis (1 point each)	Fever, tonsillar exudate, tender anterior cervical lymphadenopathy, lack of cough, 3–14 years of age
Causes of pneumonia in neonates?	GBS, *E coli*, *Listeria*
Causes of pneumonia in adults 40–65 years of age?	*S pneumoniae*, *H influenzae*, *Mycoplasma*
Treatment of tuberculosis by type	Active disease: INH + pyrazinamide + rifampin + ethambutol + vitamin B_6 Latent disease: INH for 9 months
Asplenic patients are particularly susceptible to these organisms	Encapsulated organisms—pneumococcus, meningococcus, *H influenzae*, *Klebsiella*
Patient presents with a pruritic papule with regional lymphadenopathy. Evolves into a black eschar after 7–10 days. Treatment?	Cutaneous anthrax; treat with ciprofloxacin or doxycycline
55-year-old man who is a smoker and a heavy drinker presents with a new cough and flulike symptoms. Gram stain shows no organisms. Silver stain of sputum shows gram ⊖ rods. Diagnosis?	*Legionella* pneumonia
Patient from California or Arizona presents with fever, malaise, cough, and night sweats. Diagnosis? Treatment?	Coccidioidomycosis Amphotericin B

Name the organism:	
■ Branching rods in oral infection	*Actinomyces israelii*
■ Weakly gram ⊕, partially acid-fast in lung infection	*Nocardia asteroides*
■ Alcoholic with pneumonia	*Klebsiella*
■ "Currant jelly" sputum	*Klebsiella*
■ Malignant external otitis	*Pseudomonas*

RENAL/GENITOURINARY

Treatment of hypernatremia	NS for volume resuscitation if unstable vital signs; D_5W or 0.45% NS to replace free-water loss once vitals are stable
Differential diagnosis of hypotonic hypervolemic hyponatremia	Cirrhosis, HF, nephrotic syndrome, AKI, CKD
Complication of overly rapid correction of hyponatremia (as may occur with 3% hypertonic saline therapy)	Central pontine myelinolysis (osmotic demyelination syndrome)
Most common ECG changes in hyperkalemia	Peaked T waves and widened QRS
Treatment of hyperkalemia	**C BIG K**—**C**alcium gluconate, **B**icarbonate, **I**nsulin + **G**lucose, **K**ayexalate
Most common ECG changes in hypokalemia	T-wave flattening and U waves
Most common causes of hypercalcemia	Malignancy and hyperparathyroidism
Facial spasm elicited from tapping the facial nerve (Chvostek sign), carpal spasm after arterial occlusion by a BP cuff (Trousseau sign)	Hypocalcemia
Salicylate ingestion can lead to which type(s) of acid-base disorder?	Anion gap metabolic acidosis and primary respiratory alkalosis caused by central respiratory stimulation
Acid-base disturbance commonly seen in pregnant women	Respiratory alkalosis
RTA associated with abnormal H^+ secretion and nephrolithiasis	Type I (distal) RTA
RTA associated with abnormal HCO_3^- reabsorption and rickets	Type II (proximal) RTA
RTA associated with low aldosterone state	Type IV (distal) RTA
AKI in a patient with BUN/creatinine $>$20:1 and/or FE_{Na} $<$1%	Prerenal (caused by ↓ renal perfusion)
Muddy brown casts	Acute tubular necrosis
Drowsiness, asterixis, nausea, and pericardial friction rub	Uremic syndrome seen in patients with renal failure
Hematuria, hypertension, oliguria, and RBC casts in the urine	Nephritic syndrome
Palpable purpura, arthralgias, abdominal pain, renal failure	Henoch-Schönlein purpura (IgA vasculitis)
Glomerulonephritis with deafness	Alport syndrome
Glomerulonephritis with hemoptysis	Granulomatosis with polyangiitis (Wegener) or Goodpasture syndrome
Proteinuria (≥3.5 g/day), hypoalbuminemia, edema, hyperlipidemia, and thrombosis	Nephrotic syndrome

Waxy casts in urine sediment and Maltese crosses (seen with lipiduria)	Nephrotic syndrome
Most common form of nephrotic syndrome in adults	Focal segmental glomerulosclerosis
Most common composition of kidney stone	Calcium oxalate
Test of choice for nephrolithiasis	Noncontrast CT of abdomen
Ultrasonography shows bilateral enlarged kidneys with cysts. Associated brain anomaly?	ADPKD; Cerebral aneurysm
55-year-old man presents with irritative and obstructive urinary symptoms. Treatment options?	Likely BPH; options include α-blockers (terazosin), 5α-reductase inhibitors (finasteride), or surgical intervention (TURP)
50-year-old smoker with painless hematuria	Bladder cancer
Most common histology of bladder cancer	Transitional cell carcinoma
Most common type of testicular cancer	Seminoma, a type of germ cell tumor
Testicular cancer associated with ↑ β-hCG	Choriocarcinoma
Risk factors for pyelonephritis	Pregnancy, vesicoureteral reflux, anatomic anomalies, indwelling catheters, kidney stones
Findings in primary syphilis	Painless chancre and lymphadenopathy
Findings in 3° syphilis	Tabes dorsalis, gummas, Argyll Robertson pupils, aortitis, aortic root aneurysms
Name the organism: Painful chancroid	*Haemophilus ducreyi*

MULTISYSTEM

Signs of neurogenic shock	Hypotension and bradycardia
↓ CO, ↓ PCWP, ↑ PVR	Hypovolemic shock
↓ CO, ↑ PCWP, ↑ PVR	Cardiogenic (or obstructive) shock
↑ CO, ↓ PCWP, ↓ PVR	Distributive (eg, septic or anaphylactic) shock
Treatment of septic shock	Fluids and antibiotics
Treatment of cardiogenic shock	Identify cause; inotropes (eg, dobutamine)
Treatment of hypovolemic shock	Identify cause; fluid and blood repletion
Treatment of anaphylactic shock	Epinephrine 1:1000 and diphenhydramine
The three most common causes of FUO	Infection, cancer, and autoimmune disease
SIRS criteria	Temp <36°C (96.8°F) or >38°C (100.4°F) Tachypnea >20 bpm or $PaCO_2$ <32 mm Hg Tachycardia >90 bpm WBC <4000/mm^3, >2,000/mm^3, or >10% bands

Neutropenic nadir postchemotherapy	7–10 days
Characteristics of primary Lyme disease	Erythema migrans
Characteristics of secondary Lyme disease	Arthralgias, migratory polyarthropathies, facial nerve palsy, myocarditis, third-degree heart block
Middle-aged man presents with acute-onset monoarticular joint pain and bilateral facial nerve palsy. What is the likely diagnosis, and how did he get it? Treatment?	Lyme disease, *Ixodes* tick bite, doxycycline
AIDS-defining illnesses	Esophageal candidiasis, CMV retinitis, Kaposi sarcoma, CNS lymphoma, PML, toxoplasmosis, PCP, invasive cervical/anal cancer, HIV encephalopathy
At what CD4+ cell count should *Pneumocystis jirovecii* pneumonia prophylaxis be initiated in an HIV patient? *Mycobacterium avium* complex (MAC) prophylaxis?	≤200 cells/mm^3 for *P jirovecii* (with TMP-SMX); ≤50–100 cells mm^3 for MAC (with clarithromycin/azithromycin)
ICU patient has fever and mild discomfort around central line. Culture shows budding yeast. What is the likely cause of the fever?	Candidemia may cause central line associated infection (~10%) and should not be considered a contaminant
Most frequent cause of bloodstream infections in patients with intravascular devices?	Coagulase negative staphylococci
Most common organism in burn-related infections	*Pseudomonas*
Method of calculating fluid repletion in burn patients	Parkland formula: 24-hour fluid (mL) = 4 × kg × % BSA
Name the organism: ▪ Dog or cat bite ▪ Infection in burn victims	 *Pasteurella multocida* *Pseudomonas*
Class of drugs that may cause syndrome of muscle rigidity, hyperthermia, autonomic instability, and extrapyramidal symptoms	Antipsychotics (neuroleptic malignant syndrome)
Side effects of corticosteroids	Acute mania, immunosuppression, thin skin, osteoporosis, easy bruising, myopathies
Treatment for delirium tremens	Benzodiazepines
Treatment for acetaminophen overdose	N-acetylcysteine
Treatment for opioid overdose	Naloxone
Treatment for benzodiazepine overdose	Flumazenil (monitor for withdrawal and seizures)
Treatment for neuroleptic malignant syndrome and malignant hyperthermia	Dantrolene
Causes of drug-induced SLE	INH, penicillamine, hydralazine, procainamide, chlorpromazine, methyldopa, quinidine
Burn patient presents with cherry-red, flushed skin and coma. SaO$_2$ is normal, but carboxyhemoglobin is elevated. Treatment?	Treat CO poisoning with 100% O2 or with hyperbaric O2 if poisoning is severe or the patient is pregnant
Macrocytic, megaloblastic anemia with neurologic symptoms	Vitamin B$_{12}$ deficiency

Macrocytic, megaloblastic anemia without neurologic symptoms	Folate deficiency
The following are associated with which malignancy:	
1. Acanthosis nigricans and seborrheic keratoses	1. Malignancy
2. AIDS	2. Kaposi sarcoma and non-Hogkin lymphoma
3. Neurofibromatosis type 1	3. Pheochromocytoma, neurofibroma, optic glioma
4. Neurofibromatosis type 2	4. Acoustic schwannoma
5. Tuberous sclerosis	5. Astrocytoma, cardiac rhabdomyoma
Signs of cardiac tamponade	Distended neck veins, hypotension, diminished heart sounds (Beck triad), pulsus paradoxus
Absent breath sounds, dullness to percussion, shock, flat neck veins	Massive hemothorax
Absent breath sounds, tracheal deviation, shock, distended neck veins	Tension pneumothorax
Best next step in patient with recent neck surgery, expanding neck mass/deviated trachea, and airway compromise (noisy breathing)	Wound exploration/evacuation of hematoma
Blood in urethral meatus or high-riding prostate	Bladder rupture or urethral injury
Test to rule out urethral injury	Retrograde cystourethrogram
Radiographic evidence of aortic disruption or dissection	Widened mediastinum (>8 cm), loss of aortic knob, pleural cap, tracheal deviation to the right, depression of left main stem bronchus
Radiographic indications for surgery in patients with acute abdomen	Free air under the diaphragm, extravasation of contrast, severe bowel distention, space-occupying lesion (CT), mesenteric occlusion (angiography)
Treatment for blunt or penetrating abdominal trauma in a hemodynamically unstable patient	Exploratory laparotomy
ICP in alcoholics or the elderly following head trauma. Can be acute or chronic. Crescent-shaped lesion on CT	Subdural hematoma
Head trauma with immediate loss of consciousness followed by a lucid interval and then rapid deterioration. Convex-shaped lesion on CT	Epidural hematoma

SECTION 3

TOP-RATED REVIEW RESOURCES

- How to Use the Database
- Comprehensive
- Question Banks
- Internal Medicine, Emergency Medicine, Family Medicine
- Neurology
- OB/GYN
- Pediatrics
- Psychiatry
- Surgery
- Commercial Review Courses

> *"Some books are to be tasted, others to be swallowed, and some few to be chewed and digested."*
>
> —Sir Francis Bacon

> *"Always read something that will make you look good if you die in the middle of it."*
>
> —P.J. O'Rourke

> *"So many books, so little time."*
>
> —Frank Zappa

> *"If one cannot enjoy reading a book over and over again, there is no use in reading it at all."*
>
> —Oscar Wilde

> *"Start where you are. Use what you have. Do what you can."*
>
> —Arthur Ashe

HOW TO USE THE DATABASE

This section is a database recommended clinical science review resources, question banks, and other test preparation tools marketed to medical students studying shelf exams and the USMLE Step 2 CK. For each resource, we list the **Title**, the **First Author** (or editor), the **Current Publisher,** the **Copyright Year,** the **Edition,** the **Number of Pages,** the **ISBN,** the **Approximate List Price,** the **Format** of the resource, and the **Number of Test Questions.** Finally, each resource receives a **Rating.** The resources are sorted into a comprehensive section as well as into sections corresponding to the six clinical disciplines (internal medicine, neurology, OB/GYN, pediatrics, psychiatry, and surgery). Within each section, resources are arranged first by Rating, then by Author, and finally by Title.

For this edition of *First Aid for the USMLE Step 2 CK*, the database of review resources has been completely revised, with in-depth summary comments on more than 100 books and online and mobile applications. A letter rating scale with six different grades reflects the detailed student evaluations. Each resource receives a rating as follows:

A+	Excellent for boards review
A A–	Very good for boards review; choose among the group
B+ B	Good, but use only after exhausting better resources
B–	Fair, but there are many better resources in the discipline; or low-yield subject material

The **Rating** is meant to reflect the overall usefulness of the resource in preparing for the USMLE Step 2 CK exam. This is based on a number of factors, including the following:

- Cost of the resource
- Readability of the resource
- Appropriateness and accuracy of the resource
- Quality and number of sample questions
- Quality of written answers to sample questions
- Quality and appropriateness of the illustrations (eg, graphs, diagrams, photographs)
- Length of the text (longer is not necessarily better)
- Quality and number of other resources available in the same discipline
- Importance of the discipline on the USMLE Step 2 CK exam

Please note that **the rating does not reflect the quality of the resource for purposes other than reviewing for the USMLE Step 2 CK exam.** Many resources with low ratings are well written and informative but are not ideal for USMLE Step 2 CK preparation. We have also avoided listing or commenting on the wide variety of general textbooks available in the clinical sciences.

Evaluations are based on the cumulative results of formal and informal surveys of hundreds of medical students from medical schools across the country. The summary comments and overall ratings represent a consensus opinion, but there may have been a large range of opinions or limited student feedback on any particular resource. Please note that the data listed are subject to change.

We actively encourage medical students and faculty to submit their opinions and ratings of these clinical science review books so that we can update our database (see “How to Contribute,” p. xi). In addition, we ask that publishers and authors submit review copies of clinical science review books, including new editions, and books not included in our database, for evaluation. We also solicit reviews of new books or suggestions for alternate modes of study that may be useful in preparing for the exam, such as flash cards, tutorials, commercial review courses, online resources.

DISCLAIMER/CONFLICT-OF-INTEREST STATEMENT

No material in this book, including the ratings, reflects the opinion or influence of the publisher. All errors and omissions will gladly be corrected if brought to the attention of the authors through our bloc at firstaidteam.com. Please note that USMLE-Rx and the entire *First Aid for the USMLE* series are publications by the senior authors of this book; their ratings are based solely on recommendations from the student authors of this book as well as data from the student survey and feedback forms.

TOP-RATED REVIEW RESOURCES

Comprehensive

		AUTHOR	PUBLISHER	TYPE	PRICE
A	***Boards and Beyond***	Boards and Beyond	boardsbeyond.com	Review/Test	\$24–\$399
A	***SketchyMedical Clinical***	SketchyMedical	sketchy.com/explore/medical-clinical	Review	\$300–\$600
A^-	***AMBOSS Medical Knowledge: Interactive Medical Library***	AMBOSS	amboss.com	Test	\$8–\$99
A^-	***Divine Intervention Podcast***	Divine Intervention Podcasts	divineinterventionpodcasts.com	Podcast	Free
A^-	***Master the Boards USMLE Step 2 CK***	Fischer	Kaplan Test Prep, 6th ed., 744 pages, ISBN 9781506254586	Review	\$60
A^-	***Rx Bricks***	MediQ Learning	usmle-rx.com/products/rx-bricks	Study plan	\$99–\$200
A^-	***OnlineMedEd***	OnlineMedEd	onlinemeded.org	Review	Free
A^-	***Physeo***	Physeo	physeo.com	Review	Free–\$450
B^+	***Step-Up to Medicine***	Agabegi	Lippincott Williams & Wilkins, 5th ed., 592 pages, ISBN 9781975103613	Review	\$66
B^+	***Lecturio***	Lecturio		Review	\$105–\$300
B^+	***Déjà Review: USMLE Step 2 CK***	Naheedy	McGraw Hill Medical, 3rd ed., 384 pages, ISBN 9781260464269	Review	\$27
B^+	***USMLE Step 2 Secrets***	O'Connell	Elsevier, 6th ed., 352 pages, ISBN 9780323824347	Review	\$51
B	***USMLE Step 2 Made Ridiculously Simple***	Carl	MedMaster, 6th ed., 404 pages, ISBN 9781935660231	Review	\$30

Question Banks

		AUTHOR	PUBLISHER	TYPE	PRICE
A^+	***UWorld Step 2 CK Qbank***	UWorld	uworld.com	Test	\$229–\$719
A	***AMBOSS Qbank***	AMBOSS	amboss.com	Test	\$15–\$299
A	***USMLE-Rx Step 2 CK Qmax***	MedIQ Learning	usmle-rx.com	Test	\$59–\$229
B^+	***Kaplan Qbank***	Kaplan	kaplanmedical.com	Test	\$159–\$399
B	***USMLEasy***	McGraw-Hill Education	usmle-easy.com	Test	\$39–\$169

Internal Medicine, Emergency Medicine, Family Medicine

		AUTHOR	PUBLISHER	TYPE	PRICE
A	***Case Files: Emergency Medicine***	Toy	McGraw-Hill Education, 2017, 4th ed., 672 pages, ISBN 9781259640827	Review	$39
A-	***First Aid for the Medicine Clerkship***	Kaufman	McGraw-Hill, 2021, 4th ed., 592 pages, ISBN 9781260460629	Review	$55
A-	***Emergency Medicine: PreTest Self-Assessment & Review***	Rosh	McGraw-Hill, 2016, 14th ed., 512 pages, ISBN 9780071850056	Test/500 q	$35
B+	***Step-Up to Medicine***	Agabegi	Lippincott Williams & Wilkins, 2019, 5th ed., 592 pages, ISBN 9781975103613	Review	$66
B+	***Medical Secrets***	Harward	Elsevier, 2019, 6th ed., 592 pages, ISBN 9780323478724	Review/ Test/500 q	$48
B+	***Case Files: Family Medicine***	Toy	McGraw-Hill, 2020, 5th ed., 752 pages, ISBN 9781260468595	Review	$40
B+	***Case Files: Internal Medicine***	Toy	McGraw-Hill. 2020, 6th ed., 688 pages, ISBN 9781260469967	Review	$39
B	***Medicine: PreTest Self-Assessment & Review***	Smalligan	McGraw-Hill, 2016, 14th ed., 512 pages, ISBN 978-0071850056	Test/500 q	$35

Neurology

		AUTHOR	PUBLISHER	TYPE	PRICE
A-	***Neurology: PreTest Self-Assessment & Review***	Anschel	McGraw-Hill, 2017, 9th ed., 356 pages, ISBN 978-1259586910	Test/500 q	$27
A-	***Blueprints Neurology***	Drislane	Lippincott Williams & Wilkins, 2019, 5th ed., 296 pages, ISBN 9781496387394	Review/ Test/100 q	$60
B	***Neurology Secrets***	Kass	Elsevier, 2017, 6th ed., 552 pages, ISBN 9780323359481	Review	$48

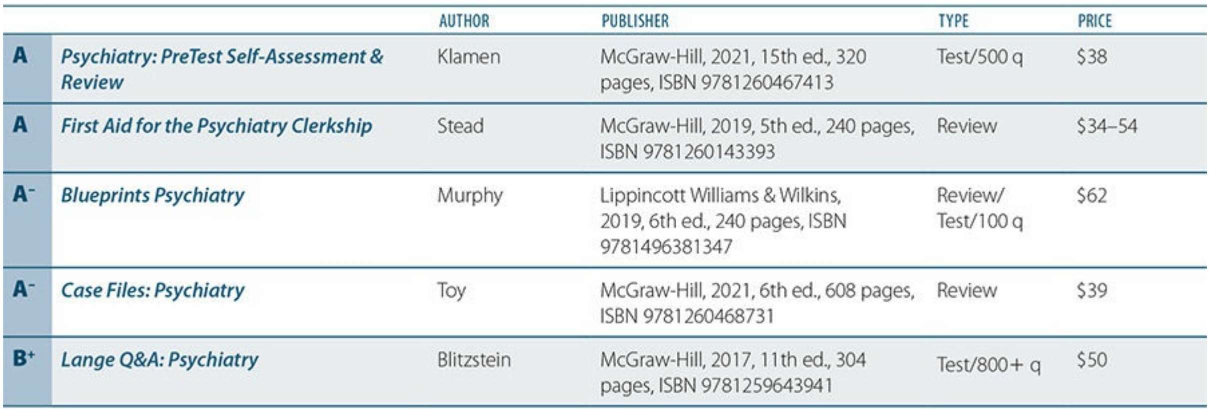
OB/GYN

		AUTHOR	PUBLISHER	TYPE	PRICE
A-	***First Aid for the Obstetrics & Gynecology Clerkship***	Kaufman	McGraw-Hill, 2018, 4th ed., 384 pages, ISBN 9781259644061	Review	$43
B+	***Blueprints Obstetrics and Gynecology***	Callahan	Lippincott Williams & Wilkins, 2018, 7th ed., 529 pages, ISBN 9781975134877	Review/ Test/150 q	$62
B+	***Obstetrics and Gynecology: PreTest Self-Assessment & Review***	Schneider	McGraw Hill, 2016, 14th ed., 358 pages, ISBN 9781259588723	Test/500 q	$42
B+	***Case Files: Obstetrics and Gynecology***	Toy	McGraw-Hill, 2021, 6th ed., 758 pages, ISBN 9781260468786	Review	$39

Pediatrics

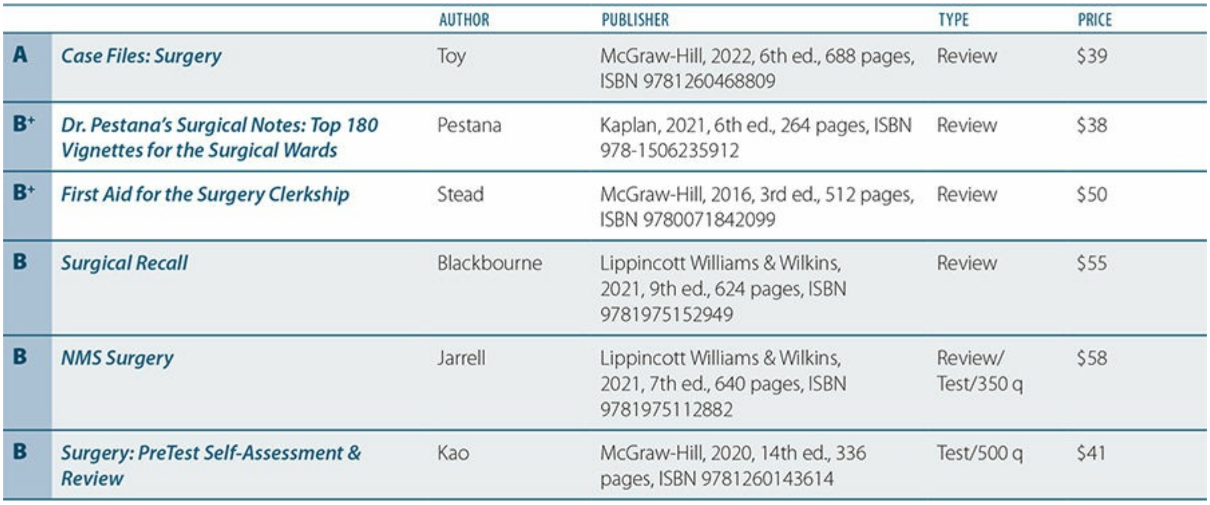
		AUTHOR	PUBLISHER	TYPE	PRICE
A-	***First Aid for the Pediatrics Clerkship***	Stead	McGraw-Hill, 2017, 4th ed., 576 pages, ISBN 9781259834318	Review	$55
A-	***Case Files: Pediatrics***	Toy	McGraw-Hill, 2021, 6th ed., 640 pages, ISBN 9781260474954	Review	$39
A-	***Pediatrics: PreTest Self-Assessment & Review***	Yetman	McGraw-Hill, 2020, 15th ed., 544 pages, ISBN 9781260440331	Test/500 q	$45
B	***Pediatric Secrets***	Polin	Elsevier, 2021, 7th ed., 688 pages, ISBN 9780323636650	Review	$51

Psychiatry



		AUTHOR	PUBLISHER	TYPE	PRICE
A	*Psychiatry: PreTest Self-Assessment & Review*	Klamen	McGraw-Hill, 2021, 15th ed., 320 pages, ISBN 9781260467413	Test/500 q	$38
A	*First Aid for the Psychiatry Clerkship*	Stead	McGraw-Hill, 2019, 5th ed., 240 pages, ISBN 9781260143393	Review	$34–54
A$^-$	*Blueprints Psychiatry*	Murphy	Lippincott Williams & Wilkins, 2019, 6th ed., 240 pages, ISBN 9781496381347	Review/ Test/100 q	$62
A$^-$	*Case Files: Psychiatry*	Toy	McGraw-Hill, 2021, 6th ed., 608 pages, ISBN 9781260468731	Review	$39
B$^+$	*Lange Q&A: Psychiatry*	Blitzstein	McGraw-Hill, 2017, 11th ed., 304 pages, ISBN 9781259643941	Test/800+ q	$50

Surgery



		AUTHOR	PUBLISHER	TYPE	PRICE
A	*Case Files: Surgery*	Toy	McGraw-Hill, 2022, 6th ed., 688 pages, ISBN 9781260468809	Review	$39
B$^+$	*Dr. Pestana's Surgical Notes: Top 180 Vignettes for the Surgical Wards*	Pestana	Kaplan, 2021, 6th ed., 264 pages, ISBN 978-1506235912	Review	$38
B$^+$	*First Aid for the Surgery Clerkship*	Stead	McGraw-Hill, 2016, 3rd ed., 512 pages, ISBN 9780071842099	Review	$50
B	*Surgical Recall*	Blackbourne	Lippincott Williams & Wilkins, 2021, 9th ed., 624 pages, ISBN 9781975152949	Review	$55
B	*NMS Surgery*	Jarrell	Lippincott Williams & Wilkins, 2021, 7th ed., 640 pages, ISBN 9781975112882	Review/ Test/350 q	$58
B	*Surgery: PreTest Self-Assessment & Review*	Kao	McGraw-Hill, 2020, 14th ed., 336 pages, ISBN 9781260143614	Test/500 q	$41

COMMERCIAL REVIEW COURSES

Although commercial preparation courses can be helpful for some students, such courses are typically costly and require significant time commitment. They are usually most effective as an organizing tool for students who feel overwhelmed by the sheer volume of material involved in Step 2 CK preparation. Note, too, that multiweek courses may be quite intense and may thus leave limited time for independent study. Also note that some commercial courses are designed for first-time test takers, while others focus on students who are repeating the exam. In addition, some courses are geared toward IMGs who want to take all three Steps in a limited amount of time.

Student experience and satisfaction with review courses are highly variable. We suggest that you discuss options with recent graduates of the review courses you are considering. In addition, course content and structure can change rapidly. Some student opinions can be found in online discussion groups.

NOTES

APPENDIX I

ABBREVIATIONS AND SYMBOLS

ABBREVIATION	MEANING
AA	2° amyloidosis
A-a	alveolar-arterial
AAA	abdominal aortic aneurysm
AB	abortion
Ab	antibody
ABC	abacavir
ABG	arterial blood gas
ABI	ankle-brachial index
ABPA	allergic bronchopulmonary aspergillosis
AC	abdominal circumference
ACE	angiotensin-converting enzyme
ACh	acetylcholine
AChR	acetylcholine receptor
AChR-Ab	acetylcholine receptor autoantibodies
ACL	anterior cruciate ligament
ACR	American College of Rheumatology
ACTH	adrenocorticotropic hormone
AD	Alzheimer dementia, Alzheimer disease
ADA	American Diabetes Association
ADH	antidiuretic hormone
ADLs	activities of daily living
ADP	adenosine diphosphate
AEDs	automated external defibrillators
AF	atrial fibrillation
AFI	amniotic fluid index
AFP	α-fetoprotein
Ag	antigen
AGCs	atypical glandular cells
AH	atypical hyperplasia
AHA	American Heart Association
AHI	apnea-hypopnea index
AI	adrenal insufficiency
AIHA	autoimmune hemolytic anemia
AIN	acute interstitial nephritis
AION	anterior ischemic optic neuropathy
AIS	androgen insensitivity syndrome
AKI	acute kidney injury
AL	1° amyloidosis
ALC	absolute lymphocyte count
ALL	acute lymphocytic leukemia
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
ALTE	apparent life-threatening event

ABBREVIATION	MEANING
AMA	American Medical Association
AMD	age-related macular degeneration
AML	acute myelogenous leukemia, acute myeloid leukemia
AMS	altered mental status
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANCA	antineutrophil cytoplasmic antibody
ANOVA	analysis of variance
ANS	autonomic nervous system
anti-CCP	anticyclic citrullinated peptide
anti-CTLA-4	anti-cytotoxic T-lymphocyte–associated antigen 4
anti-TPO	antithyroid peroxidase
APC	activated protein C
APL	acute promyelocytic leukemia
APS	antiphospholipid syndrome
aPTT	activated partial thromboplastin time
AR	aortic regurgitation
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
ARNI	angiotensin receptor neprilysin inhibitor
ARPKD	autosomal recessive polycystic kidney disease
ART	antiretroviral therapy
ARVD	arrhythmogenic right ventricular dysplasia
AS	ankylosing spondylitis, aortic stenosis
ASA	acetylsalicylic acid
aPTT	activated partial thromboplastin time
ASC-H	atypical squamous cells suspicious for high-grade dysplasia
ASC-US	atypical squamous cells of undetermined significance
ASCVD	atherosclerotic cardiovascular disease
ASD	autism spectrum disorder, atrial septal defect
ASO	antistreptolysin O
AST	aspartate aminotransferase
AT	antithrombin
ATG	antithymocyte globulin
ATLS	dvanced trauma life support
ATN	acute tubular necrosis
ATRA	all-trans-retinoic acid
AUB	abnormal uterine bleeding
AV	atrioventricular
aVF	augmented vector foot
aVL	augmented vector left
AVM	arteriovenous malformation
AVN	avascular necrosis

ABBREVIATION	MEANING
AVNRT	atrioventricular nodal reentry tachycardia
aVR	augmented vector right
AVRT	atrioventricular reentrant tachycardia
AZT	zidovudine
BAC	bronchioalveolar carcinoma
BBB	blood–brain barrier
BCC	basal cell carcinoma
BCG	bacillus Calmette–Guérin
β-hCG	β-human chorionic gonadotropic
biPAP	bilevel positive airway pressure
BMD	bone mineral density
BMI	body mass index
BMT	bone marrow transplantation
BP	blood pressure
BPD	biparietal diameter
BPH	benign prostatic hyperplasia
bpm	beats per minute
BPP	biophysical profile
BRUE	brief resolved unexplained event
BSA	body surface area
BSO	bilateral salpingo-oophorectomy
BUN	blood urea nitrogen
BW	birth weight
C1INH	C1 inhibitor
CA	cancer antigen
CABG	coronary artery bypass graft surgery
CAD	coronary artery disease
CADherins	Ca^{2+}-dependent adhesion proteins
CAH	congenital adrenal hyperplasia
CAM	Confusion Assessment Method
$CaNa_2EDTA$	edetate calcium disodium
CBC	complete blood cell count
CBD	common bile duct
CCB	calcium channel blocker
CCP	cyclic citrullinated peptide
CEA	carcinoembryonic antigen, carotid endarterectomy
CEP	chronic eosinophilic pneumonia
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CFU	colony forming unit
CGD	chronic granulomatous disease
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
CHADS-VASc	CHF, HTN, Age ≥75, diabetes, stroke or TIA history, vascular disease, age 65–74, sex category
CHD	congenital heart disease
CHF	congestive heart failure
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CJD	Creutzfeldt-Jakob disease
CK	creatine kinase
CKD	chronic kidney disease
CLASBIs	central line-associated bloodstream infections
CLL	chronic lymphocytic leukemia

ABBREVIATION	MEANING
CMC	carpometacarpal (joint)
CML	chronic myelogenous leukemia
CMP	comprehensive metabolic panel
CMR	cardiovascular magnetic resonance imaging
CMV	cytomegalovirus
CN	cranial nerve
CNS	central nervous system
CO_2	carbon dioxide
CO	cardiac output
COMT	catechol-O-methyltransferase
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
CP	cerebral palsy
CPAP	continuous positive airway pressure
CPPD	calcium pyrophosphate deposition disease
CPR	cardiopulmonary resuscitation
Cr	creatine
CREEP	colitis, retinitis, esophagitis, encephalitis, pneumonitis
CREST	calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia
CRH	corticotropin-releasing hormone
CRL	crown-rump length
CRP	c-reactive protein
CRVO	central retinal vein occlusion
CSA	central sleep apnea
CSF	cerebrospinal fluid
CSM	carotid sinus massage
CSS	cytokine storm syndrome
CST	contraction stress test
CTA	computed tomography angiography, CT angiography
CVA	cerebrovascular accident, costovertebral angle
CVAT	costovertebral angle tenderness
CVID	common variable immunodeficiency
CVS	chorionic villus sampling
CXR	x-ray of the chest
CXVD	cardiovascular disease
D&C	dilation and curettage
d4T	stavudine
D_5W	dextrose 5% water
DA	dopamine, embryonic age
DAAs	direct-acting antivirals
DAI	diffuse axonal injury
DAP	diaminopyridine
DBP	diastolic blood pressure
DCIS	ductal carcinoma in situ
DCM	dilated cardiomyopathy
ddC	zalcitabine
DDD	depersonalization/derealization disorder
ddI	didanosine
DES	diethylstilbestrol
DEXA	dual-energy x-ray absorptiometry
DFA	direct fluorescent antibody
DH	dermatitis herpetiformis
DHEA	dehydroepiandrosterone

ABBREVIATION	MEANING
DHEAS	dehydroepiandrosterone sulphate
DHR	dihydrorhodamine
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DIP	distal interphalangeal (joint)
DIT	diiodotyrosine
DKA	diabetic ketoacidosis
DLB	dementia with Lewy bodies
DLCO	diffusing capacity of the lung
DM	dermatomyositis, diabetes mellitus; (may be type 1 [type 1 DM] or type 2 [type 2 DM])
DMARD	disease-modifying antirheumatic drug
DMDD	disruptive mood dysregulation disorder
DNase	deoxyribonuclease
DNI	do not intubate
DNR	do not resuscitate
DOAC	direct oral anticoagulant
DPL	diagnostic peritoneal lavage
DPLD	diffuse parenchymal lung disease
DPP	dipeptidyl peptidase
DRE	digital rectal exam
DRESS	drug reactions with eosinophilia and systemic symptoms
ds	double-stranded
DTRs	deep tendon reflexes
DTs	delirium tremens
DVT	deep venous thrombosis
eADA	erythrocyte adenosine deaminase
EBV	Epstein-Barr virus
EC	emergency contraception
ECF	extracellular fluid
ECMO	extracorporeal membrane oxygenation
ECT	electroconvulsive therapy
ED	erectile dysfunction
EDTA	ethylenediaminetetraacetic acid
EEG	electroencephalography
EF	erythema multiforme
EFW	estimated fetal weight
EGD	esophagogastroduodenoscopy
eGFR	estimated glomerular filtration rate
EGPA	eosinophilic granulomatosis with polyangiitis
EHEC	enterohemorrhagic *Escherichia coli*
ELISA	enzyme-linked immunosorbent assay
EMG	electromyography
ENT	ears, nose, and throat
Epi	epinephrine
EPO	erythropoietin
EPSs	extrapyramidal symptoms
ER	estrogen receptor
ERCP	endoscopic retrograde cholangiopancreatography
ERV	expiratory reserve volume
ESAs	erythropoiesis-stimulating agents
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
ET	endotracheal

ABBREVIATION	MEANING
ETEC	enteropathogenic *E coli*
EtOH	ethanol
EUS	endoscopic ultrasound
FA	fanconi anemia
FAB	fragment antigen binding antibodies
FAP	familial adenomatous polyposis
FAS	fetal alcohol syndrome
FAST	focused abdominal sonography for trauma
FDG-PET	fluorodeoxyglucose -positron emission tomography FDPs fibrin degradation products
Fe_{Na}	fractional excretion of sodium
FEV1	forced expiratory volume in 1 second
FFP	fresh frozen plasma
FGR	fetal growth restriction
FHR	fetal heart rate
Fio_2	fraction of inspired oxygen
FISH	fluorescence in situ hybridization
FIT	fecal immunochemical test
FL	femur length
FLAIR	fluid-attenuated inversion recovery
FNA	fine-needle aspiration
FNH	focal nodular hyperplasia
FOBT	fecal occult blood test
FOOSH	fall onto an outstretched hand
FPIAP	food protein-induced allergic proctocolitis
FRC	functional residual capacity
FSH	follicle-stimulating hormone
FTA-ABS	fluorescent treponemal antibody absorption
FTC	emtricitabine
FTD	frontotemporal dementia
FTT	failure to thrive
5-FU	fluorouracil
FUO	fever of unknown origin
FVC	forced vital capacity
FXN	frataxin
G6P	glucose-6-phosphate
G6PD	glucose-6-phosphate dehydrogenase
GA	gestational age
GABA	gamma-aminobutyric acid
GAD	generalized anxiety disorder, glutamic acid decarboxylase
GALT	galactose-1-phosphate uridyl transferase
GAS	group A *Streptococcus*
GBM	glioblastoma
GBS	group B streptococcus
GCS	Glasgow Coma Scale
G-CSF	granulocyte colony stimulating factor
GERD	gastroesophageal reflux disease
GFAP	glial fibrillary acid protein
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase, gamma-glutamyl transpeptidase
GHB	gamma-hydroxybutyric acid
GI	gastrointestinal
GLP	glucagon-like peptide

ABBREVIATION	MEANING
GLP1	glucagon-like peptide-1
GM-CSF	granulocyte-macrophage colony stimulating factor
GnRH	gonadotropin-releasing hormone
GPA	granulomatosis with polyangiitis
GTD	gestational trophoblastic disease
GTT	glucose tolerance test
GU	genitourinary
GVHD	graft-versus-host disease
H	hemagglutinin, histamine
H&E	hematoxylin and eosin
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
Hb	hemoglobin
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigens
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCM	hypertrophic cardiomyopathy
HCT	hematopoietic cell transplantation
Hct	hematocrit
HCV	hepatitis C virus
HD	Huntington disease
HDL	high-density lipoprotein
HDN	hemolytic disease of the newborn
HDV	hepatitis D virus
HER2	human epidermal growth factor 2
HES	hypereosinophilic syndrome
HEV	hepatitis E virus
HF	heart failure
HFmrEF	heart failure with moderately reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
HHS	hyperglycemic hyperosmolar syndrome
HHV	human herpes virus
5-HIAA	5-hydroxyindoleacetic acid
Hib	*Haemophilus influenzae* type b
HIDA	hydroxy iminodiacetic acid
HIF	hypoxia-inducible factor
HIPPA	Health Insurance Portability and Accountability Act
HIT	heparin-induced thrombocytopenia
HL	Hodgkin lymphoma
HLA	human leukocyte antigen
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitor (statin)
HMWK	high-molecular-weight kininogen
HNPCC	hereditary nonpolyposis colorectal cancer
HOCM	hypertrophic obstructive cardiomyopathy
HPV	human papilloma virus
HR	hazard ratio, heart rate
HRT	hormone replacement therapy
HS	hereditary spherocytosis
HSIL	high-grade squamous intraepithelial lesion
HSP	Henoch-Schönlein purpura

ABBREVIATION	MEANING
HSV	herpes simplex virus
HAART	highly active antiretroviral therapy
5HT	5-hydroxytryptamine
HT	hydroxytryptamine
HTLV	human T-cell lymphotropic virus
HTN	hypertension
HUS	hemolytic uremic syndrome
I^-	iodide
I	iodine
IADLs	instrumental activities of daily living
IBD	inflammatory bowel disease, inflammatory bowel disorder
IBI	invasive bacterial infection
IBS	irritable bowel syndrome
IBS-C	IBS that is constipation predominant
IBS-D	IBS that is diarrheal predominant
IC	inspiratory capacity
ICA	internal carotid artery
ICD	implantable cardiac defibrillator
ICF	intracellular fluid
ICH	intracranial hemorrhage
ICHD	International Classification of Headache Disorders
ICP	intracranial pressure
ICS	intercostal space
ICSs	inhaled corticosteroids
ICU	intensive care unit
IE	infective endocarditis
IFN	interferon
IFN-α	interferon-α
IgE	immunoglobin E
IGF	insulin-like growth factor
IgG	immunoglobin G
IGRAs	interferon gamma release assays
IIH	idiopathic intracranial hypertension
IL	interleukin
LD	interstitial lung disease
IM	intramuscular
INH	isoniazid
INO	internuclear ophthalmoplegia
INR	International Normalized Ratio
IOP	intraocular pressure
IPF	idiopathic pulmonary fibrosis
IRV	inspiratory reserve volume
Itp	idiopathic thrombocytopenic purpura
IUD	intrauterine device
IUGR	intrauterine growth restriction
IUI	intrauterine insemination
IV	intravenous, intravenously
IVC	inferior vena cava
IVDU	intravenous drug use
IVF	in vitro fertilization
IVIG	intravenous immunoglobulin
JIA	juvenile idiopathic arthritis
JPS	juvenile polyposis syndrome
JRA	juvenile rheumatoid arthritis

ABBREVIATION	MEANING
JVD	jugular venous distention
JVP	jugular venous pressure
KOH	potassium hydroxide
KS	Kaposi sarcoma
KSHV	Kaposi sarcoma–associated herpesvirus
L	lumbar
LAA	left atrial appendage
LAE	left atrial enlargement
LAM	lymphangioleiomyomatosis
LAMA	long-acting muscarinic antagonist
LAP	leukocyte alkaline phosphatase
LBBB	left bundle branch block
LBO	large bowel obstruction
LBP	low back pain
LCIS	lobular carcinoma in situ
LCL	lateral collateral ligament
LDH	lactate dehydrogenase
LEEP	loop electrosurgical excision procedure
LES	lower esophageal sphincter
LFT	liver function test
LGV	lymphogranuloma venereum
LH	luteinizing hormone
LIP	lymphoid interstitial pneumonia
LLQ	left lower quadrant
LLSB	lower left sternal border
LM	lateral meniscus
LMN	lower motor neuron
LMP	last menstrual period
LMWH	low-molecular-weight heparin
LP	lumbar puncture
LQTS	long QT syndrome
LR	lactated Ringer's, likelihood ratio
LSD	lysergic acid diethylamide
LSIL	low-grade squamous intraepithelial lesion
LTOT	long-term oxygen therapy
LUQ	left upper quadrant
LV	left ventricle, left ventricular
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVOT	left ventricular outflow tract obstruction
M	monoclonal
MAC	membrane attack complex, *mycobacterium avium* complex
MALT	mucosa-associated lymphoid tissue
MAO	monoamine oxidase
MAP	mean arterial pressure
MART	maintenance and reliever therapy
MCA	middle cerebral artery
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCL	medial collateral ligament
MCP	metacarpophalangeal (joint)
MCV	mean corpuscular volume
MDD	major depressive disorder
MDE	major depressive episode

ABBREVIATION	MEANING
MDS	myelodysplastic syndromes
MELD	model for end-stage liver disease
MEN1	multiple endocrine neoplasia type 1
MEN2A	multiple endocrine neoplasia type 2A
MEN2B	multiple endocrine neoplasia type 2B
MERS	Middle East respiratory syndrome
MG	myasthenia gravis
MGUS	monoclonal gammopathy of undetermined significance
MHA-TP	microhemagglutination assay–*Treponema pallidum*
MI	myocardial infarction
MIBG	metaiodobenzylguanidine (scan)
MIT	monoiodotyrosine
MLF	medial longitudinal fasciculus
MM	medial meniscus, multiple myeloma
MMA	methylmalonic acid
MMF	mycophenolate mofetil
MMR	measles, mumps, and rubella (vaccine)
MMSE	Mini-Mental State Examination
MOA	mechanism of action
MoCA	Montreal Cognitive Assessment
MODY	maturity-onset diabetes of the young
MoM	multiple of the median
6-MP	mercaptopurine
MPGN	membranoproliferative glomerulonephritis
MPTP	1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine
MR	magnetic resonance, mitral regurgitation
MRA	magnetic resonance angiography
MRCP	magnetic resonance cholangiopancreatography
MRSA	methicillin-resistant *Staphylococcus aureus*, methicillin-resistant S *aureus*
MS	multiple sclerosis
MSAFP	maternal serum α-fetoprotein
msec	millisecond
MSM	men who have sex with men
MTB	*mycobacterium tuberculosis*
mTOR	mechanistic target of rapamycin
MTP	metatarsophalangeal (joint)
MUA	manual uterine aspiration
MuSK	muscle-specific kinase
MVC	motor vehicle collision
MVP	mitral valve prolapse
N	neuraminidase
NAAT	nucleic acid amplification testing
NAFLD	nonalcoholic fatty liver disease
NAPLLR	nephritis-associated plasmin receptor
NASH	nonalcoholic steatohepatitis
NAT	nonaccidental trauma
NCCT	noncontrast computed tomography
NE	norepinephrine
NEC	necrotizing enterocolitis
NEXUS	National Emergency X-Radiography Utilization Study
NF	neurofibromatosis
NG	nasogastric
NHL	non-Hodgkin lymphoma

ABBREVIATION	MEANING
NIF	negative inspiratory force
NIHSS	National Institutes of Health Stroke Scale
NK	natural killer (cell)
NMDA	N-methyl-D-aspartate
NMJ	neuromuscular junction
NMS	neuroleptic malignant syndrome
NNT	number needed to treat
NOAC	novel oral anticoagulant
NPD	nasal potential difference
NPH	neutral protamine Hagedorn insulin, normal pressure hydrocephalus
NPO	nil per os (nothing by mouth)
NPPV	noninvasive positive-pressure ventilation
NPV	negative predictive value
NRDS	neonatal respiratory distress syndrome
NRTIs	nucleoside/nucleotide reverse transcriptase inhibitors
NS	normal saline
NNRTI	non-nucleoside reverse transcriptase inhibitor
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small cell lung cancer
NSGCT	nonseminomatous germ cell tumor
NST	nonstress test
NTD	neural tube defect
NYHA	New York Heart Association
O&P	ova and parasite exam
OCD	obsessive-compulsive disorder, osteochondritis dissecans
OCP	oral contraceptive pill
OCPD	obsessive-compulsive personality disorder
ODD	oppositional defiant disorder
OE	otitis externa
OGTT	oral glucose tolerance test
OH	hydroxy
OHS	obesity hypoventilation syndrome
OI	osteogenesis imperfecta
ONSF	optic nerve sheath fenestration
OR	odds ratio, operating room
OI	opportunistic infection
ORIF	open reduction and internal fixation
OSA	obstructive sleep apnea
OTC	over the counter
PA	posteroanterior, pulmonary artery
Paco$_2$	partial pressure of carbon dioxide
PAD	peripheral arterial disease
PAH	pulmonary arterial hypertensin
Pao$_2$	partial pressure of oxygen
PAP	positive airway pressure
PAPP-A	pregnancy-associated plasma protein A
PAS	periodic acid–Schiff
PBC	primary biliary cholangitis
PBF	peripheral blood film
PC	pressure control
PCC	prothrombin complex concentrate
PCL	posterior cruciate ligament
PCom	posterior communicating
PCOS	polycystic ovarian syndrome

ABBREVIATION	MEANING
PCP	phencyclidine hydrochloride, *Pneumocystis carinii* pneumonia
PCR	polymerase chain reaction
PCSK9	proprotein convertase subtilisin/kexin type 9
PCV	polycythemia vera
PCWP	pulmonary capillary wedge pressure
PD	Parkinson disease, programmed death
PDA	patent ductus arteriosus
PDD	Parkinson disease dementia, pervasive developmental disorder, premenstrual dysphoric disorder
PDE	phosphodiesterase
PDE5	phosphodiesterase type 5
PDGF	platelet-derived growth factor
PD-L1	programmed death-ligand 1
PEEP	positive end-expiratory pressure
PET	positron emission tomography
PF	platelet factor
PFT	pulmonary function test
PG	prostaglandin
PGB	porcelain gallbladder, porphobilinogen
PGE_1	prostaglandin E_1
PGI_2	prostacyclin
PH	pulmonary hypertension
PICA	posterior inferior cerebral artery
PID	pelvic inflammatory disease
PIP	peak inspiratory pressure, proximal interphalangeal (joint)
PKU	phenylketonuria
PLA	phospholipase
PLCH	pulmonary Langerhans cell histiocytosis
PM	polymyositis
PMI	point of maximal impulse
PMN	polymorphonuclear (leukocyte)
PNET	primitive neuroectodermal tumor
PNH	paroxysmal nocturnal hemoglobinuria
PO_2	partial pressure of oxygen
PO	per os (by mouth, oral)
POC	products of conception
POD	postoperative day
POEM	peroral endoscopic myotomy
POLST	physician orders for life-sustaining treatment
PPD	purified protein derivative [of tuberculin]
PPE	personal protective equipment
P_{Peak}	peak inspiratory pressure
PPIs	proton pump inhibitors
P_{Plat}	plateau pressure
PPRF	paramedian pontine reticular formation
PPROM	preterm primary rupture of membranes
PPV	positive predictive value, positive pressure ventilation
PPV23	23-polyvalent pneumococcus vaccine
PR	per rectum, progesterone receptor, proteinase
pRBC	packed red blood cell
PrEP	preexposure prophylaxis
PT	prothrombin time
PCWP	pulmonary capillary wedge pressure
PROM	premature rupture of membranes

ABBREVIATION	MEANING
PS	pronator syndrome
PSA	prostate-specific antigen
PSC	primary sclerosing cholangitis
PSGN	post-streptococcal glomerulonephritis
PSP	progressive supranuclear palsy
PT	prothrombin time
PTH	parathyroid hormone
PTHrP	parathyroid hormone–related protein
PTSD	post-traumatic stress disorder
PTT	partial thromboplastin time
PTU	propylthiouracil
PUD	peptic ulcer disease
PVC	premature ventricular contraction
PVR	peripheral vascular resistance
QTc	QT interval corrected for extremes in heart rate
RA	rheumatoid arthritis
RAAS	renin-angiotensin-aldosterone system
RAI	radioactive iodine
RAIU	radioactive iodine uptake
RAS	renal artery stenosis
RAST	serum radio-allergosorbent test
RBBB	right bundle branch block
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RCTs	randomized controlled trials
RDS	respiratory distress syndrome
RDW	red cell distribution width
REM	rapid eye movement
RERAs	respiratory effort–related arousals
RF	rheumatoid factor
RHD	rheumatic heart disease
RLQ	right lower quadrant
RNP	ribonucleoprotein
ROC	receiver operating characteristic
ROM	range of motion, rupture of membranes
RPR	rapid plasma reagin
RR	relative risk, risk ratio, respiratory rate
rRNA	ribosomal RNA
RSV	respiratory syncytial virus
RTA	renal tubular acidosis
RT-PCR	reverse transcription quantitative polymerase chain reaction
RT-QuIC	real-time quaking-induced conversion
RUQ	right upper quadrant
RV	residual volume, right ventricle
RVH	right ventricular hypertrophy
RVOT	right ventricular outflow tract
S	sacral
SA	sinoatrial
SAAG	serum-ascites albumin gradient
SAB	spontaneous abortion
SABA	short-acting β_2-agonists
SAH	subarachnoid hemorrhage
SAMA	short-acting muscarinic antagonist
SaO_2	oxygen saturation

ABBREVIATION	MEANING
SARS	severe acute respiratory syndrome
SBFT	small bowel follow-through
SBO	small bowel obstruction
SBP	spontaneous bacterial peritonitis, systolic blood pressure
SCC	squamous cell carcinoma
SCD	subacute combined degeneration, sudden cardiac death
SCDs	sequential compression socks
SCFE	slipped capital femoral epiphysis
SCID	severe combined immunodeficiency
SD	standard deviation
SDB	sleep-disordered breathing
SDS	Shwachman-Diamond syndrome
SERM	selective estrogen receptor modulator
SES	socioeconomic status
SGLT	sodium-glucose transporter (SGLT)
SGLT-2	sodium-glucose transporter 2
SIADH	syndrome of inappropriate secretion of ADH
SIBO	small intestinal bacterial overgrowth
SIMV	synchronized intermittent mandatory ventilation
SIRS	systemic inflammatory response syndrome
SJS	Stevens-Johnson syndrome
SLE	systemic lupus erythematosus
Sm	Smith
SMA	spinal muscular atrophy, superior mesenteric artery
SNRI	serotonin-norepinephrine reuptake inhibitor
SNS	sympathetic nervous system
SOB	shortness of breath
SOFA	sequential organ failure assessment
sOsm	serum osmolality
SPF	sun protection factor
Spo_2	saturation of peripheral oxygen
SS	somatostatin
SSRI	selective serotonin reuptake inhibitor
SSSS	staphylococcal scalded-skin syndrome
STD	sexually transmitted disease
STE	ST elevation
STI	sexually transmitted infection
SVC	superior vena cava
SVT	supraventricular tachycardia
T_3	triiodothyronine
T_4	thyroxine
TACE	transarterial chemoembolization
TAH/BSO	total abdominal hysterectomy/bilateral salpingo-oophorectomy
TAF	tenofovir alafenamide
TAPVR	total anomalous pulmonary venous return
TAR	thrombocytopenia absent radius
TAVR	transcatheter aortic valve replacement
TB	tuberculosis
TBG	thyroxine-binding globulin
TBI	traumatic brain injury
TBW	total body water
3TC	lamivudine
TCA	tricyclic antidepressant
TD	tardive dyskinesia

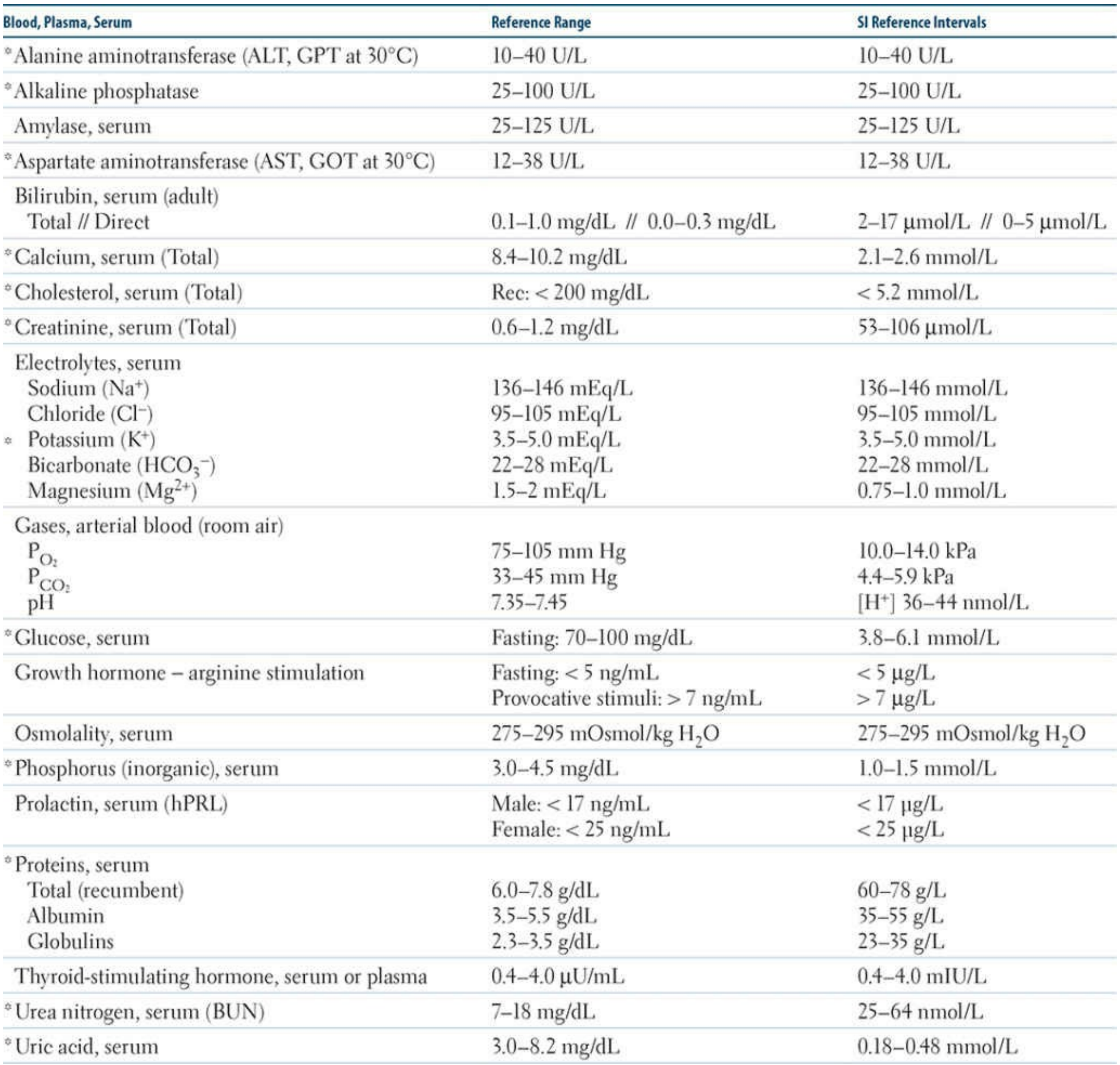
ABBREVIATION	MEANING
TDF	tenofovir disoproxil fumarate
TdT	terminal deoxynucleotidyl transferase
TEN	toxic epidermal necrolysis
TFT	thyroid function test
TGF	transforming growth factor
Th cells	T-helper cells
THC	tetrahydrocannabinol
THI	transient hypogammaglobulinemia of infancy
TIA	transient ischemic attack
TIBC	total iron-binding capacity
TIPS	transjugular intrahepatic portosystemic shunt
TLC	total lung capacity
TM	tympanic membrane
TMP-SMX	trimethoprim-sulfamethoxazole
TNF	tumor necrosis factor
TNM	tumor, node, metastasis (staging)
TOA	tubo-ovarian abscess
TOF	tetralogy of Fallot
TORCH	toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex
tPA	tissue plasminogen activator
TPAL	(number of) term deliveries, preterm deliveries, abortuses, and living children
TP-EIA	*treponema pallidum* enzyme immunoassay
TPN	total parenteral nutrition
TPO	thrombopoietin, thyroid peroxidase
TP-PA	*Treponema pallidum* particle agglutination
TPR	total peripheral resistance
TR	tricuspid regurgitation
TRH	thyrotropin-releasing hormone
TSC	tuberous sclerosis complex
TSH	thyroid-stimulating hormone
TSI	thyroid-stimulating immunoglobulin
TSS	toxic shock syndrome
TSST-1	toxic shock syndrome toxin 1
TST	tuberculin skin test
TTE	transthoracic echocardiogram
TTP	thrombotic thrombocytopenic purpura
TURP	transurethral resection of the prostate
TXA_2	thromboxane A_2
UA	urinalysis

ABBREVIATION	MEANING
UAG	urine anion gap
UC	ulcerative colitis
UFH	unfractionated heparin
UMN	upper motor neuron
URI	upper respiratory infection
US	ultrasound
USPSTF	United States Preventive Services Task Force
UTI	urinary tract infection
UV	ultraviolet
V/Q	ventilation/perfusion
VACTERL-H	vertebral abnormalities, anal atresia, cardiac (heart) defects, tracheoesophageal fistula, esophageal atresia, renal (kidney) and radial abnormalities, limb abnormalities, hydrocephalus
VC	vital capacity, volume control
VCUG	voiding cystourethrogram
VDRL	Venereal Disease Research Laboratory
VEGF	vascular endothelial growth factor
VF	ventricular fibrillation
VGCC	voltage-gated calcium channel
VIN	vulvar intraepithelial neoplasia
VMA	vanillylmandelic acid
VMAT	vesicular monoamine transporter
VMAT2	vesicular monoamine transporter 2
VOC	vaso-occlusive crisis
VP	ventriculoperitoneal
VR	vascular resistance
VRSA	vancomycin-resistant S *aureus*
VSD	ventricular septal defect
VT	ventricular tachycardia
VTE	venous thromboembolism
VUR	vesicoureteral reflux
vWD	von Willebrand disease
vWF	von Willebrand factor
VZV	varicella zoster virus
WHO	World Health Organization
WMA	World Medical Association
WPW	Wolff-Parkinson-White
XR	x-ray
ZDV	zidovudine

APPENDIX II

COMMON LABORATORY VALUES

* = Included in the Biochemical Profile (SMA-12)



Blood, Plasma, Serum	Reference Range	SI Reference Intervals
*Alanine aminotransferase (ALT, GPT at 30°C)	10–40 U/L	10–40 U/L
*Alkaline phosphatase	25–100 U/L	25–100 U/L
Amylase, serum	25–125 U/L	25–125 U/L
*Aspartate aminotransferase (AST, GOT at 30°C)	12–38 U/L	12–38 U/L
Bilirubin, serum (adult)		
Total // Direct	0.1–1.0 mg/dL // 0.0–0.3 mg/dL	2–17 µmol/L // 0–5 µmol/L
*Calcium, serum (Total)	8.4–10.2 mg/dL	2.1–2.6 mmol/L
*Cholesterol, serum (Total)	Rec: < 200 mg/dL	< 5.2 mmol/L
*Creatinine, serum (Total)	0.6–1.2 mg/dL	53–106 µmol/L
Electrolytes, serum		
Sodium (Na^+)	136–146 mEq/L	136–146 mmol/L
Chloride (Cl^-)	95–105 mEq/L	95–105 mmol/L
* Potassium (K^+)	3.5–5.0 mEq/L	3.5–5.0 mmol/L
Bicarbonate (HCO_3^-)	22–28 mEq/L	22–28 mmol/L
Magnesium (Mg^{2+})	1.5–2 mEq/L	0.75–1.0 mmol/L
Gases, arterial blood (room air)		
P_{O_2}	75–105 mm Hg	10.0–14.0 kPa
P_{CO_2}	33–45 mm Hg	4.4–5.9 kPa
pH	7.35–7.45	$[H^+]$ 36–44 nmol/L
*Glucose, serum	Fasting: 70–100 mg/dL	3.8–6.1 mmol/L
Growth hormone – arginine stimulation	Fasting: < 5 ng/mL	< 5 µg/L
	Provocative stimuli: > 7 ng/mL	> 7 µg/L
Osmolality, serum	275–295 mOsmol/kg H_2O	275–295 mOsmol/kg H_2O
*Phosphorus (inorganic), serum	3.0–4.5 mg/dL	1.0–1.5 mmol/L
Prolactin, serum (hPRL)	Male: < 17 ng/mL	< 17 µg/L
	Female: < 25 ng/mL	< 25 µg/L
*Proteins, serum		
Total (recumbent)	6.0–7.8 g/dL	60–78 g/L
Albumin	3.5–5.5 g/dL	35–55 g/L
Globulins	2.3–3.5 g/dL	23–35 g/L
Thyroid-stimulating hormone, serum or plasma	0.4–4.0 µU/mL	0.4–4.0 mIU/L
*Urea nitrogen, serum (BUN)	7–18 mg/dL	25–64 nmol/L
*Uric acid, serum	3.0–8.2 mg/dL	0.18–0.48 mmol/L

Cerebrospinal Fluid	**Reference Range**	**SI Reference Intervals**
Cell count	0–5/mm^3	0–5 × 10^6/L
Glucose	40–70 mg/dL	2.2–3.9 mmol/L
Proteins, total	< 40 mg/dL	< 0.40 g/L
Hematologic		
Erythrocyte count	Male: 4.3–5.9 million/mm^3 Female: 3.5–5.5 million/mm^3	4.3–5.9 × 10^{12}/L 3.5–5.5 × 10^{12}/L
Erythrocyte sedimentation rate (Westergen)	Male: 0–15 mm/hr Female: 0–20 mm/hr	0–15 mm/hr 0–20 mm/hr
Hematocrit	Male: 41–53% Female: 36–46%	0.41–0.53 0.36–0.46
Hemoglobin, blood	Male: 13.5–17.5 g/dL Female: 12.0–16.0 g/dL	135–175 g/L 120–160 g/L
Hemoglobin, plasma	< 4 mg/dL	< 0.62 µmol/L
Leukocyte count and differential		
Leukocyte count	4,500–11,000/mm^3	4.5–11.0 × 10^9/L
Segmented neutrophils	54–62%	0.54–0.62
Band forms	3–5%	0.03–0.05
Eosinophils	1–3%	0.01–0.03
Basophils	0–0.75%	0–0.0075
Lymphocytes	25–33%	0.25–0.33
Monocytes	3–7%	0.03–0.07
Mean corpuscular hemoglobin	25–35 pg/cell	0.39–0.54 fmol/cell
Mean corpuscular hemoglobin concentration	31%–36% Hb/cell	4.8–5.6 mmol Hb/L
Mean corpuscular volume	80–100 µm^3	80–100 fL
Partial thromboplastin time (activated)	25–40 sec	25–40 sec
Platelet count	150,000–400,000/mm^3	150–400 × 10^9/L
Prothrombin time	11–15 sec	11–15 sec
Reticulocyte count	0.5–1.5% of RBCs	0.005–0.015
Urine		
Creatinine clearance	Male: 97–137 mL/min Female: 88–128 mL/min	97–137 mL/min 88–128 mL/min
Osmolality	50–1200 mOsmol/kg H_2O	50–1200 mOsmol/kg H_2O
Proteins, total	< 150 mg/24 hr	< 0.15 g/24 hr
Other		
Body mass index	Adult: 19–25 kg/m^2	19–25 kg/m^2

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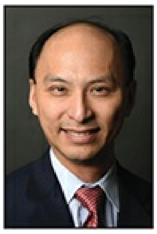
About the Editors

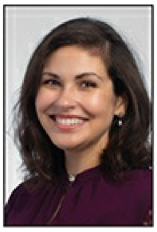


Tao Le, MD, MHS

Tao developed a passion for medical education as a medical student. He has edited more than 15 titles in the *First Aid* series. In addition, he is Founder and Chief Education Officer of USMLE-Rx for exam preparation and ScholarRx for sustainable, global medical education. As a medical student, he was editor-in-chief of the University of California, San Francisco (UCSF) *Synapse*, a university newspaper with a weekly circulation of 9000. Tao earned his medical degree from UCSF in 1996 and completed his residency training in internal medicine at Yale University and fellowship training at Johns Hopkins University. Tao subsequently went on to cofound Medsn, and served as its chief medical officer. He is currently chief of adult allergy and immunology at the University of Louisville.

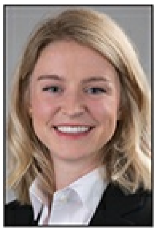
Mona Ascha, MD

Mona has a passion for plastic surgery, medical education, data science, research reproducibility, and providing care for marginalized populations. She is currently completing a gender-affirmation surgery fellowship at Johns Hopkins University and is earning her Master's degree in Data Science. Mona has worked on the *First Aid* team since 2015, contributing to multiple projects; she has found the work to be incredibly fulfilling and rewarding. In her spare time, Mona likes to read about statistics, code, and build her GitHub repo with personal projects. She is an avid tennis player and marathoner, having completed nine marathons to date. She also enjoys spending time in coffee shops reading and people watching, brushing up on her French, top rope rock climbing, taking improv classes, eating donuts, and getting crazy manicures.



Marina Boushra, MD

Marina was born in Cairo, Egypt to a family that taught her a deep love of medicine and a passion for education. She completed her residency training in Emergency Medicine at East Carolina University in Greenville, North Carolina and her fellowship training in Critical Care Medicine at the Cleveland Clinic in Cleveland, Ohio. She is now an emergency medicine physician and intensivist at the Cleveland Clinic, where she hopes to instill in learners the same passion for medicine and education with which she was fortunate to grow up. Her medical interests include ED-ICU transitions, obstetric and toxicologic emergencies, medical education, and microbiology. Marina has been involved with the First Aid and ScholarRx Teams since 2014. Outside the hospital, she enjoys being overly competitive at board and card games, writing prose, and binging TV shows with her husband and their alarmingly growing number of cats.



Caroline Coleman, MD

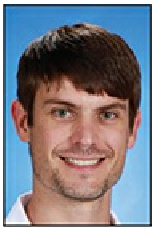
Caroline is a current PGY-3 in the J. Willis Hurst Internal Medicine Residency at Emory University in Atlanta. She grew up in Florida before moving to Georgia to pursue her undergraduate degree in economics from the University of Georgia and medical degree at Emory University School of Medicine. She is interested in a career as an academic hospitalist where she can pursue her interests of clinical reasoning, medical education, and illustrations and graphic design.

Vikas Bhushan, MD

Vikas is a writer, editor, entrepreneur, and retired teleradiologist. In 1990 he conceived and authored the original *First Aid for the USMLE Step 1*. His entrepreneurial endeavors include a student-focused medical publisher (S2S), an e-learning company (medschool.com), and an ER teleradiology practice (24/7 Radiology). Trained on the Left Coast, Vikas completed a bachelor’s degree at the University of California Berkeley; an MD with thesis at UCSF; and a diagnostic radiology residency at UCLA. His eclectic interests include cryptoeconomics, information design, and avoiding a day job. Always finding the long shortcut, Vikas is an adventurer, knowledge seeker, and occasional innovator. He enjoys intermediate status as a kiteboarder and father, and strives to raise his three children as global citizens.

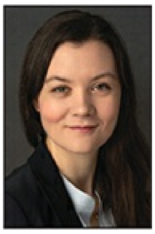
Abhishek Bhardwaj, MD

Abhishek is a pulmonologist and intensivist in Southern California. He was born and raised in India and earned his medical degree from Kasturba Medical College in Manipal, India. He completed his Internal Medicine training at Mercy Catholic Medical Center in Philadelphia and his fellowship training in Pulmonary and Critical Care Medicine at the Cleveland Clinic in Cleveland, Ohio. In addition, he also pursued a Resuscitation Fellowship at the University of Pennsylvania and is currently earning a Master's degree in Clinic Research. He is passionate about improving critical care accessibility and outcomes, medical education, and humanism in medicine. As a foreign medical graduate, he understands the unique challenges of international medical students and enjoys mentoring the next generation of physicians. He is also an avid drone videographer, podcast host, competitive table tennis player, and creative writer. He strives to never miss a sunset with his two sons and prioritizes time with his family.



Daniel Griffin, DO

Dan is an intensivist at Saint Francis Medical Center in Cape Girardeau, Missouri. He was born and raised in Mississippi where he attended Mississippi College for his undergraduate degree and William Carey University College of Osteopathic Medicine for his medical degree. He completed internal medicine residency at Magnolia Regional Health Center in Corinth, MS and pulmonary/critical care fellowship at University of Missouri at Kansas City. Over the last six years, he has been involved in various projects with the First Aid team. In his spare time, Dan enjoys exercising and spending time with his family.



Stephanie Jones, PhD

Stephanie is a biological illustrator in Tumwater, Washington and earned her PhD in genetics and molecular biology from Emory University. During her dissertation research, Stephanie pursued her passion for visual scientific communication and created numerous illustrations that have been featured in scientific publications, medical education, science outreach, and

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professional branding. She strives to show students and professionals how fascinating and accessible science can be.

Kimberly Kallianos, MD

Originally from Atlanta, Kimberly graduated from the University of North Carolina at Chapel Hill in 2006 and from Harvard Medical School in 2011. She completed her radiology residency and fellowship at UCSF and is currently an Assistant professor of Clinical Radiology at UCSF in the cardiac and pulmonary imaging section.